# ORGANIC FUNCTIONAL GROUP PREPARATIONS

## Second Edition

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# III

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# PREFACE

The purpose of this series is to provide the organic chemist with a convenient and updated source of useful preparative procedures that have been described in the literature (journals and patents). In this volume, we cover synthetic methods for the generation of 13 functional groups.

For this second edition, the literature has been reviewed from 1971 to the present and includes new information where pertinent, new and expanded tables of data, additional preparations, and recent references from the journal and patent literature. A unique feature of this work is that the United States and foreign patent literature is frequently cited. It is these patent references which should be of great value to the industrial chemist.

Information about safety precautions is given where available. We particularly continue to urge the laboratory worker to check the toxicity and other potential hazards of all reagents, intermediates, and final products. The reader is urged to check the Material Safety Data Sheets (MSDS) from the suppliers of chemicals and to inform assistants of this information. The reader should consult and become familiar with the "NIOSH Registry of Toxic Effects of Chemical Substances 1981–1982 Edition" (edited by R. L. Tatken and R. J. Lewis, Sr., published by the United States Department of Health and Human Services, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio, 40226; June 1983). We caution those anticipating scale-up work to first undertake extensive tests to ensure that this can be done safely. The heat of reaction among other things should be determined to ensure that a runaway reaction will not take place in the equipment used. Many of the preparations have not been checked either by us or by an independent laboratory for hazards and toxicity and are given here only for information purposes. We do not warrant the preparations against any safety or toxic hazards and assume no liability with respect to the use of the preparations or of the products.

We wish to express our gratitude to our wives and families for their patience, understanding, and encouragement during all phases of the preparation of this manuscript. We also express our appreciation to the production staff of Academic Press for their help in the various phases of publication of this volume.

We again were very fortunate to have Ms. Emma Moesta type the revisions for each of the chapters of this second edition and to provide us with a highly professional manuscript. Her sincere and dedicated efforts on our behalf will always be remembered and very much appreciated.

STANLEY R. SANDLER
WOLF KARO

# FROM THE PREFACE TO THE FIRST EDITION

Volume III describes 13 additional functional groups and presents them as in previous volumes with detailed preparative examples.

The format of this volume follows that of Volumes I and II. Where possible, the preparative details for each functional group are divided according to their reaction type (condensation, elimination, oxidation, reduction). The literature is up-to-date and each chapter carries an extensive reference list.

In many cases, it was felt that suitable general preparative details have not been reliably developed for their inclusion at this time in this text. We urge our readers to correspond with us and present information that would be of general interest to others.

We certainly hope that our discussions, although brief at times, help to point out the need for further work in areas lacking preparative information. If we have inspired anyone to further investigate these areas, we certainly have accomplished a major goal of this text.

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## 1. INTRODUCTION

Acetals possess a terminal 1,1-diether group, and ketals possess the same type of group in an internal position. These groups may be thought to be diether derivatives of the parent geminal dihydroxy compounds (hydrated aldehydes or ketones).

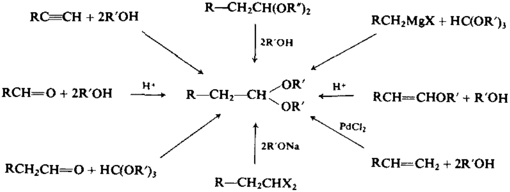
A wide variety of methods are available for the preparation of acetals and ketals, and the most important synthetic routes are summarized in Schemes 1 and 2.

Acetals and ketals are important functional groups that find use in the preparation of novel heterocyclic compounds, in polymers, and in the protection of carbonyl compounds or alcohols. Acetals and ketals are stable under basic conditions but hydrolyze easily under acidic conditions to the starting carbonyl compound and alcohol.

A brief review of the chemistry of acetals appears in the literature [1]. Recently the chemistry of the condensation products of glycerol with aldehyde and ketones to give cyclic aldehydes has been reviewed [2a].

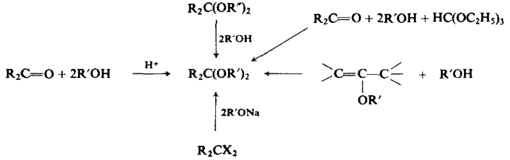
SCHEME 1

Preparation of Acetals

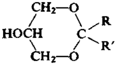


SCHEME 2

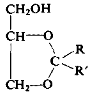
Preparation of Ketals



The *Chemical Abstracts* nomenclature is used for most of the acetals described in this chapter. The compounds are named either as dialkoxy derivatives or as derivatives of acetals or ketals. Confusion exists in the earlier literature on naming cyclic acetals. For example, the acetals prepared from glycerol and an aldehyde were at one time referred to as 1,2- or 1,3-alkylidene (or arylidene) glycerol; however, today they are named as shown below:

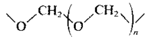


**(old) 1,3-Alkylidene glycerol**
**(new) 2-Alkyl-*m*-dioxan-5-ol**



**(old) 1,2-Alkylidene glycerol**
**(new) 2-Alkyl-4-hydroxymethyl-1,3-dioxolane**

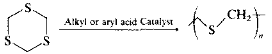
Polyacetals prepared from formaldehyde are engineering thermoplastics, which have found use in traditional metal applications. Some trade names of these polymers are Delrin acetal homopolymer (DuPont); Celcon acetal copolymer (Celanese/Hoechst); Duracon acetal copolymer (Celanese and Diacel—joint venture); Tenac acetal homopolymer by Asahi Chemical in Japan; and Ultraform acetal copolymer jointly by BASF and Degussa, in the Federal Republic of Germany. The polymers have the basic structure shown below:



The number average molecular weight of the commerical polymers are in the range of 25,000–75,000. The chemistry of these polyacetal resins has been reviewed [2b].

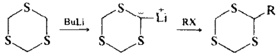
Where possible, this chapter also includes preparations of thioacetals and thioketals.

Asahi Chemical has also reported a process for the production of thioacetal polymers prepared by the polymerization of trithiane [2c].



(1)

Trithiane can be used as a means to introduce the aldehyde functionality by reacting with halides, as shown below [2d].



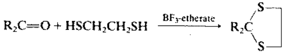
(2)

$$\xrightarrow[CH_3OH]{HgCl_2/HGO} (CH_3O)_2CHR \xrightarrow{H_3O^+} RCH{=}O \qquad (3)$$

50–55% overall yield

Thioacetals and thioketals have also been reported to have organoleptic properties [2e].

Thioketals have been widely used as protective groups for ketones.



(4)

The protective thioketal group can be removed to regenerate the ketone. In addition, the thioketals can be desulfurized with Raney nickel to give the overall conversion $R_2C{=}O \rightarrow R_2CH_2$.

The pyrolysis of acetals has been used to give vinyl ethers. For example [2f,g, h],

$$CH_3CH_2CH(OCH_3)_2 \longrightarrow CH_3CH{=}CH{-}OCH_3 \qquad (5)$$

## 2. CONDENSATION REACTIONS

Acetals or ketals can be prepared by several types of condensation reactions involving either the condensation of alcohols, ortho esters, or dihalomethylene compounds with a variety of starting materials, as described below. The most common method of preparing acetals or ketals involves the condensation of alcohols with either aldehydes or ketones, respectively. This reaction is highly recommended since the yields are usually high, as shown in Table I. However, the other methods are also widely used, and their use often depends on the starting material at hand or the structure of the acetal or ketal desired.

Acetals and ketals with side chain groups or unsaturated groups can be made to undergo a variety of condensation reactions, and some of the important ones are described in Section 3.

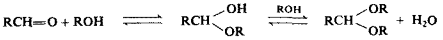
### A. Condensation of Alcohols with Aldehydes and Ketones

Aldehydes and ketones react with alcohols to give an equilibrium mixture of the acetal and water (Eq. 6). The reaction is shifted toward completion by azeotropic removal of water or by using special drying agents. The reaction usually proceeds without the aid of catalysts in the case of aldehydes, but ketones require acids in order to obtain the ketals.

$$RR'C{=}O + 2R''OH \rightleftharpoons RR'C(OR'')_2 + H_2O \qquad (6)$$

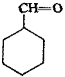
For aldehydes: $R$ = alkyl or aryl, $R' = H$
For ketones: $R = R'$ or $R \neq R'$ = alkyl or aryl
$R''$ = alkyl as in diols, glycols, polyols, and hemiacetals as in β-D(+)-glucose

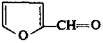
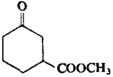
In some cases, evidence has been reported to indicate that hemiacetals are first formed by the reaction of alcohols in the presence of aldehydes or ketones in neutral, basic, or acidic solutions [3] (Eq. 7).



$$RCH{=}O + ROH \rightleftharpoons RCH\begin{matrix}OH\\OR\end{matrix} \underset{}{\overset{ROH}{\rightleftharpoons}} RCH\begin{matrix}OR\\OR\end{matrix} + H_2O \qquad (7)$$

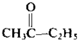
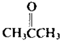
## TABLE I
PREPARATION OF ACETALS AND KETALS BY THE CONDENSATION OF ALCOHOLS WITH ALDEHYDES OR KETONES

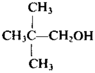
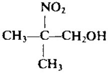
| RCH=O (moles) | R′₂C=O (moles) | ROH (moles) R = | Catalyst (gm) | Solvent (ml) | Reaction conditions Temp. (°C) | Time (hr) | Yield (%) | B.p., °C (mm Hg) or m.p., °C | $n_D$ (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|
| $CH_2{=}O$ (paraformaldehyde) (0.5) | — | $n$-$C_4H_9$ (1.0) | $FeCl_2$ (2) | — | 117–118 | 10 | 77 | 180.5 | — | *a* |
| $CH_3CH{=}O$ (11.4) | — | $C_2H_5$ (21.7) | $CaCl_2$ (164) | — | 25 | 24–48 | 61–64 | 101.0–103.5 | — | *b* |
| (1.14) | — | $CH_2{=}CH{-}CH_2$ (2.3) | — | — | 0 | 13.5 | 68.2 | 148–149 | — | *c* |
| $CH_2{=}CHCH{=}O$ (2.0) | — | $C_2H_5$ (4.3) | HCl Saturated | — | 0 | 2 | 34 | 58–62 (8) | — | *d* |
| (1.0) | — | $CH_2{=}CH{-}CH_2$ (1.0) | PTSA (0.17) | Pet. ether (150) | 70–80 | 24 | 72 | 75 (28) | 1.4380 (20) | *e* |
| (2.8) | — | $C_2H_5$ (9.0) | $NH_4Cl$ (10) | — | 30–80 | 5 | 31–39 | 75–78 (16) | 1.4067 (20) | *f* |
| (1.36) | — | $C_2H_5$ (5.56) | HCl (0.7) | — | 0 | 48–60 | Acrolein acetal<br>24–30<br>β-Ethoxypropionaldehyde diethyl acetal<br>52 | 45 (24)<br>80–84 (21) | — | *g* |
|  (1.0) | — | $CH_3$ (5.0) | — | — | — | — | 93 | 63 (25) | 1.4402 (20) | *h* |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| (1.0) | — | $C_2H_5$ (5.0) | — | — | — | — | 78 | 94–94 (12) | 1.4399 (20) | *h* |
|  (1.0) | — | $C_2H_5$ (6.0) | HCl (0.0012) | — | 25 | 24 | 24 | 72–79 (16) | — | *i* |
| Br—$CH_2$=O (7.0) | — | $C_2H_5$ (14.0) | — | — | 10–13 | 48 | 23–27 | 65–68 (12) | — | *j* |
| — | $(CH_3)_2C$=O (4.09) | Glycerol (1.09) | PTSA–$H_2O$ (3.0) | Skellysolve (b.p. 35°–55°C) (300) | 35–55 | 21–36 | 87–90 | 80–81 (11) | 1.4339 (25) | *k* |
| $CH_2$=CHCH=O (3.2) | — | Glycerol (3.0) | $H_2SO_4$ (0.05) | $C_6H_6$ (600) | 80 | 3 | 83 | 70–72 (2) | 1.4647 (20) | *l* |
| $C_6H_{13}$CH=O (0.5) | — | Ethylene glycol (0.5) | $H_2SO_4$ (40%) (0.25) | | 100 | 10 | 58 | 197–202 | — | *m* |
| — |  (0.328) | Ethylene glycol (0.61) | PTSA (0.05) | $C_6H_6$ (20) | 80 | 5.5 | 92 | 99–104 (1.2–1.3) | 1.4641 (27.5) | *n* |
| $CH_2$=CHCH=O (2.0) | — | 2-Methyl-2,4-pentanediol (2.0) | HCl (73) | $CHCl_3$ (350) | −15 to −10 | 2–3 | 94 | 71 (5)<br>2-(2-Chloroethyl-4,4,6-trimethyl-*1,3-dioxane* | — | *o* |
| (1.1) | — | 2-Methyl-2,4-pentanediol (1.0) | PTSA 5.0 | $C_6H_3$ (300) | 80 | 2.5 | 98.5 | 62–64 (18)<br>2-Vinyl-4,4,6-trimethyl-1,3-dioxane | 1.4381 (20) | *p* |

(*continues*)

TABLE I (*continued*)

| RCH=O (moles) | $R_2'C=O$ (moles) | ROH (moles) R = | Catalyst (gm) | Solvent (ml) | Reaction conditions | | Yield (%) | B.p., °C (mm Hg) or m.p., °C | $n_D$ (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Temp. (°C) | Time (hr) | | | | |
| — |  $CH_3\overset{O}{\overset{\|}{C}}-C_2H_5$ (11.1) | $CH_3C(CH_2OH)_3$ (8.0) | PTSA (2) | $C_6H_6$ (400) | 80 | 40 | — | 125 (14) | 1.4549 (25) | *q* |
| $CH_2=O$ (paraformaldehyde) (34.8) | — | $HOCH_2(CH_2)_2CH_2OH$ (33.5) | PTSA (5) | — | 80 | 2–3 | 90 | 119 (760) | 1.4275 (25) | *r* |
| — |  $CH_3\overset{O}{\overset{\|}{C}}CH_3$ (4.0) | Glycerol (1.1) | Advawet (0.4) +$CaC_2$ (84) | — | 58 | 4–5 | 84 | 79–81 (11) | 1.4325 (25) | *s* |
| $C_6H_5CH=O$ (1.38) | — | $C(CH_2OH)_4$ (1.32) | HCl (6.6) | $H_2O$ (1300) | 25 | 5–6 | 73–77 | 134–135 | — | *t* |
| (1.0) | — | $C(CH_2OH)_4$ (1.0) | HCl (5.0) | $H_2O$ (1000) | 25 | 29–30 | 80 | 133.5 | — | *u* |
| (0.027) | | Dipentaerythritol (0.018) | PTSA (0.1) | $C_6H_6$ (100) | 80 | 1–2 | 60 | 166 | — | *v* |
| *m*$(NO_2)C_6H_4CH=O$ (1.5–1.68) | — | $CH_3OH$ (20) | HCl (1) | — | 25 | 120 | 76–85 | 141–143 (8) | — | *w* |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $C_6H_5CH{=}O$<br>(0.037) | — | $CH_3C(CH_3)_2{-}CH_2OH$<br>(0.074) | PTSA<br>(0.075) | $C_6H_6$<br>(90) | 80 | 1–2 | 68 | 102 (0.8) | 1.4682<br>(22) | *x* |
| (0.65) | — | $CH_3{-}C(NO_2)(CH_3){-}CH_2OH$<br>(1.0) | PTSA<br>(1.0) | Toluene<br>(150) | 110 | 16 | 12 | 63 | — | *y* |

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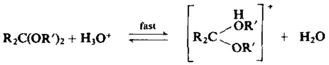
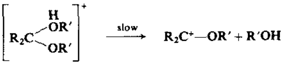
[a] A. I. Vogel, *J. Chem. Soc.* 616 (1948). [b] H. Adkins and B. H. Nissen, *Org. Syn. Coll.* **1**, 1 (1932); *J. Amer. Chem. Soc.* **44**, 2749 (1922). [c] C. D. Hurd and M. A. Pollack, *J. Amer. Chem. Soc.* **60**, 1905 (1938). [d] E. J. Witzemann, W. L. Evans, H. Hass, and E. F. Schroeder, *Org. Syn. Coll.* **2**, 137 (1943). Product Structure: $Cl{-}CH_2CH_2CH(OC_2H_5)_2$. [e] R. F. Fischer and C. W. Smith, *J. Org. Chem.* **25**, 319 (1960). [f] C. G. Alberti and R. Sallazo, *Org. Syn. Coll.* **3**, 371 (1955). [g] W. T. Simpson, *J. Amer. Chem. Soc.* **71**, 754 (1949); F. P. Pingert, *Org. Syn.* **25**, 1 (1945). [h] R. E. Dunbar and H. Adkins, *J. Amer. Chem. Soc.* **56**, 442 (1934). [i] H. Adkins, J. Semb, and L. M. Bolander, *J. Amer. Chem. Soc.* **53**, 1853 (1931). [j] A. N. Dey, *J. Chem. Soc.* 1057 (1937). [k] M. Renoll and M. S. Newman, *Org. Syn. Coll.* **3**, 502 (1955). [l] R. F. Fischer and C. W. Smith, *J. Org. Chem.* **25**, 319 (1960). [m] H. Hibbert and J. A. Timm, *J. Amer. Chem. Soc.* **46**, 1283 (1924). [n] H. O. House, R. A. Latham, and C. D. Slater, *J. Org. Chem.* **31**, 2667 (1966). [o] R. F. Fischer and C. W. Smith, U.S. Pat. 2,888,492 (1959). [p] R. F. Fischer and C. W. Smith, U.S. Pat. 2,987,524 (1961). [q] H. F. McShane, Jr., U.S. Pat. 2,854,486 (1958). [r] D. B. Pattison, *J. Org. Chem.* **22**, 662 (1957). [s] M. M. Maglio and C. A. Burger, *J. Amer. Chem. Soc.* **68**, 529 (1946). [t] C. H. Issidorides and R. Gulen, *Org. Syn. Coll.* **4**, 679 (1963). [u] E. Bograchov, *J. Amer. Chem. Soc.* **72**, 2268 (1950). [v] E. Bograchov, *J. Amer. Chem. Soc.* **72**, 2274 (1950). [w] R. N. Icke, C.E. Redemann, B. B. Wisegarver, and G. A. Alles, *Org. Syn. Coll.* **3**, 644 (1955) [x] C. A. Mackenzie and J. H. Stocker, *J. Amer. Chem. Soc.* **77**, 3148 (1955). [y] M. Senkus, *J. Amer. Chem. Soc.* **69**, 1380 (1947).

Acetals and ketals are converted to aldehydes or ketones by hydrolysis in acid solution [4a–c] (Eqs. 8–10)



(8)



(9)

$$R_2C^+{-}OR' + H_2O \xrightarrow{\text{fast}} R_2C{=}O + R'OH + H_3O^+ \tag{10}$$

Acids such as hydrogen chloride [5], sulfuric acid [6a], acid ion-exchange resins [6b,c], phosphoric acid [7], or *p*-toluenesulfonic acid [8a,b] catalyze the acetal or ketal formation reaction and aid in the water removal. This is especially important in the case of ketones. A Dean-Stark trap is useful when azeotropic removal of water is attempted [9]. After the reaction, the acid catalyst is neutralized, and the acetal or ketal product is distilled [10a]. Ammonium chloride and ammonium nitrate also have been reported to act as catalysts [10b].

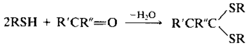
Some metal salts have also been reported to act as catalysts for acetal formation. For example, Adams and Adkins earlier reported both that ferric chloride is a good catalyst for methylal formation and that calcium chloride catalyzes acetal formation [10a]. Acetaldehyde dibutylacetal has been reported to be prepared by adding acetaldehyde (6.4 moles) at 0–5°C to 12 moles butyl alcohol and 1.45 moles of $CaCl_2$. The mixture was shaken for 12 hours to give 78–80% $MeCH(OBu)_2$ [10c]. Molecular sieves have also been reported to be effective catalysts for the preparation of acetals and ketals in high yield [10d]. Calcium sulfate is also reported as an effective catalyst in the presence of HCl for the preparation of ketals such as acetone dimethyl ketal (2,2-dimethoxy propane) [10e].

Primary alcohols give better yields of acetals than secondary or tertiary alcohols [11]. Highly branched aldehydes or ketones also give poor yields of acetals or ketals, respectively [11].

The preparation of acetal (1,1-diethoxyethane) and butylal are described in Preparations 2-1 and 2-2, respectively.

Some additional examples illustrating the condensation of aldehydes and ketones with alcohols are shown in Table I.

Mercaptans can be reacted with aldehydes and ketones to give thioacetals and thioketals (see Table II for preparation of mercaptals):

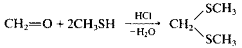


$$2RSH + R'CR''{=}O \xrightarrow{-H_2O} R'CR''C\begin{matrix} SR \\ SR \end{matrix} \qquad (11)$$

where R″ = H, alkyl or aryl; R and R′ = alkyl or aryl.

Table II describes the preparation of various mercaptals.

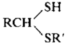
Formaldehyde mercaptals are reported to be stable even when methyl mercaptan was used [11b]. Also reported are formaldehyde mercaptals of



$$CH_2{=}O + 2CH_3SH \xrightarrow[-H_2O]{HCl} CH_2\begin{matrix} SCH_3 \\ SCH_3 \end{matrix} \qquad (12)$$

$C_2H_5SH$ $(CH_3)_2CHSH$ and $C_6H_5SH$ were prepared in 71–92% yields [11b].

Dithiohemiacetals(I) have also been reported to be prepared from aldehydes, mercaptans, and $Na_2S$ [11c].



$$RCH\begin{matrix} SH \\ SR' \end{matrix}$$

38% yield when $R = R' = CH_3$

I

## 2-1. *Preparation of Acetal (1,1-Diethoxyethane)* [12a,b]

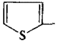
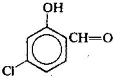
$$CH_3CH{=}O + 2C_2H_5OH \longrightarrow CH_3CH(OC_2H_5)_2 + H_2O \qquad (13)$$

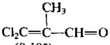
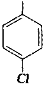
To a pressure bottle containing 20 gm (0.18 mole) of anhydrous calcium chloride is added 105 gm of 95% (2.17 moles) ethanol and the mixture cooled to 8°C. Then 50 gm (1.14 moles) of cold acetaldehyde is slowly poured down the wall of the bottle. The bottle is closed and shaken vigorously for 5–10 min, with cooling if necessary. The mixture is allowed to stand at room temperature with intermittent shaking for 24 hr. The upper layer, which has separated, weighs 128–129 gm. It is washed three times with 30–40 ml of water. The organic layer is dried over 3 gm of anhydrous potassium carbonate and distilled through a 1 ft column, to afford 70–72 gm (59–60%), b.p. 101–103.5°C. The low-boiling fractions are washed again with water, dried and again fractionally distilled to give another 9.0–9.5 gm (7.9–8.1%), b.p. 101–103.5°C. Therefore, the total yield amounts to 79–81.5 gm (67–69%), $n_D^{25}$ 1.3819, $d_4^{20}$ 0.8314.

A procedure identical to 2-1, but using 132 gm (2.28 moles) of allyl alcohol in place of ethanol, affords allyl acetal (110.5 gm) in 68.2% yield, b.p. 146–150°C [13].

## TABLE II

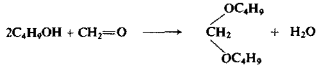
### PREPARATION OF MERCAPTALS

| RCH═O (mole) | RSH (mole) | Catalyst (g) | Solvent (ml) | Reaction conditions | | Yield % | B.p.,°C (mm Hg) or m.p.,°C | $_{t}n_{\mathrm{D}}$ (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Temp. °C | Time (hr) | | | | |
| Homocyclocitral (25g)/181 | $CH_3$- (25g.)/108 | PTSA (0.5) | Cyclohexane (200) | 0 | 8 | — | — | — | *a*<br>*b* |
| $CH_3CH{=}O$ (1.0) | *t*-$C_4H_9$- (2.2) | HCl (gas) | — | 25 | 2 | — | 135–136 | 1.4848 (20) | *c* |
| *n*-$C_3H_7CH{=}O$ (1.0) |  (2.0) | HCl (gas) | — | 75 | 2 | 58 | 173–176 (2.0) | — | *d* |
|  | —$CH_2COOH$ | PTSA or HCl (gas) | $C_6H_2$ | 78–80 | — | — | M.P. 131–132 | — | *e* |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| $CH_2{=}O$ | $t$-$C_{12}$ | HCl (gas) | — | — | — | — | — | — | *f* |
|  $Cl_2C{=}C(CH_3){-}CH{=}O$<br>(0.185) |  (0.40) | HCl (gas) | Pet-ether | 76 | 3 | 75 | 65–67 | — | *g* |
| $CH_2{=}O$ (paraformaldehyde)<br>(1.0) | $t$-$C_4H_9$<br>(2.0) | HCl (gas) | — | 25–30 | 3 | 88.5 | — | 1.4903<br>(25) | *h* |
| Piperonaldehyde | $n$-$C_8H_{17}$- | | Pet-ether at 100–120°C | 100–120 | 3.25 | 92 | — | — | *i* |

[a] A. O. Pittet, R. Muralidhara, K. P. Miller, D. Luccarelli, Jr. and M. H. Vock, U.S. Pat. 4,658,067 (4/14/87). [b] A. O. Pittet, R. Muralidhara, *K. P. Miller, D. Luccarelli, Jr. and M. H. Vock, U.S. Pat. 4,565,707 (1/21/86).* [c] W. W. Crouch, U.S. Pat. 2,571,114 (10/16/51). [d] J. W. Brooks, U.S. Pat. 2,600,838 (6/17/52). [e] L. Reiner, E. Fells and V. S. Miller, U.S. Pat. 2,724,721 (11/22/55). [f] D. L. Cotte, D. W. Young, A. J. Morway and P. V. Smith, U.S. Pat. 2,874,192 (2/17/59). [g] D. G. Kundiger and G. F. Morris, U.S. Pat. 2,922,821 (1/26/60). [h] B. D. Vineyard, U.S. Pat. 3,478,107 (11/11/69). [i] L. Hopkins, H. Stephenson and D. R. Maciver, U.S. Pat. 3,509,182 (4/28/70).

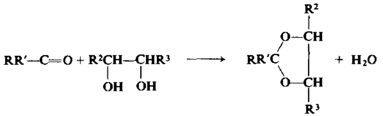
### 2.2. *Preparation of* n-*Butylal (Dibutoxymethane)* [14]



$$2C_4H_9OH + CH_2{=}O \longrightarrow CH_2(OC_4H_9)_2 + H_2O \qquad (14)$$

A flask containing 15 gm (0.5 mole) of paraformaldehyde, 74 gm (1.0 mole) of *n*-butyl alcohol, and 2.0 gm of anhydrous ferric chloride is refluxed for 10 hr. The lower layer of 3–4 ml of material is discarded and then 50 ml of 10% aqueous sodium carbonate solution is added to remove the ferric chloride as ferric hydroxide. The product is shaken with a mixture of 40 ml of 20% hydrogen peroxide and 5 ml of 10% sodium carbonate solution at 45°C in order to remove any remaining aldehyde. The product is also washed with water, dried, and distilled from excess sodium metal to afford 62 gm (78%), b.p. 180.5°C (760 mm Hg).

Glycols, such as ethylene, propylene, or trimethylene glycols, react with aromatic and aliphatic aldehydes and ketones to form cyclic acetals [6a,b, 15].

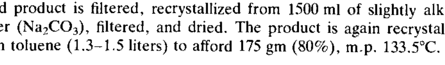


(15)

Some examples of the condensation of ethylene glycol with carbonyl compounds to give cyclic acetals (1,3-dioxolanes) are shown in Table III.

The reaction of benzaldehyde with pentaerythritol to give monobenzalpentaerythritol is described in Preparation 2-3.

### 2-3. *Preparation of Monobenzalpentaerythritol* [16a,b]



(16)

To a flask containing a solution of 136.0 gm (1.0 mole) of pentaerythritol in 1 liter of water (25–29°C) is added 5.0 ml of concentrated hydrochloric acid and then 106 gm (1.0 mole) of benzaldehyde is dropwise added (approx. 2–3 hr). The mixture is stirred for 3–5 hr and then the precipitated product is filtered, recrystallized from 1500 ml of slightly alkaline water ($Na_2CO_3$), filtered, and dried. The product is again recrystallized from toluene (1.3–1.5 liters) to afford 175 gm (80%), m.p. 133.5°C.

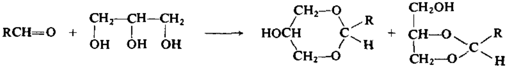
## TABLE III

### CONDENSATION PRODUCTS OF ETHYLENE GLYCOL WITH CARBONYL COMPOUNDS

| | | | | | Dioxolanes | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Molar refraction | |
| Carbonyl compound | Time required (hr) | Yield (%) | B.p., °C (mm Hg) | Formula | $d_4^{20}$ | $n_D^{20}$ | Calc. | Found |
| Heptaldehyde | 2.5 | 81.0 | 94 (20) | $C_9H_{13}O_2$ | 0.9077[a] | 1.43060[a] | 44.85 | 44.70 |
| Benzaldehyde | 2.5 | 82.7 | 101 (10) | $C_9H_{10}O_2$ | 1.1156[a] | 1.52696[a,b] | 41.25 | 41.53 |
| 4-Methoxybenzaldehyde | 3.25 | 84.4 | 158–60 (17) | $C_{10}H_{12}O_3$ | 1.1776[a] | 1.53622[a] | 47.51 | 47.79 |
| 2-Chlorobenzaldehyde | 1.00 | 83.5 | 150–52 (16) | $C_9H_9O_2Cl$ | 1.2639[g] | 1.2631[g] | 56.11[g] | 45.99[g] |
| Methyl isobutyl ketone | 4.0 | 84.0 | 48 (10) | $C_8H_{16}O_2$ | 0.908 | 1.4180 | 40.23 | 40.00 |
| Mesityl oxide[c] | 5.5 | 66.9 | 156 (760) | $C_8H_{14}O_2$ | 0.9471[h] | 1.43963[h] | 39.76[h] | 39.52[h] |
| Pinacolone | 4.5 | 80.5 | 139 (760) | $C_8H_{16}O_2$ | 0.9239 | 1.42356 | 40.23 | 39.77 |
| Cyclohexanone | 1.5 | 84.5 | 65 (10) | $C_8H_{14}O_2$ | 1.026 | 1.4580[d,e] | 38.07 | 37.67 |
| 2-Methylcyclohexanone | 1.4 | 83.3 | 82 (15) | $C_9H_{16}O_2$ | 1.0000[a] | 1.45579[a] | 42.65 | 42.41 |
| Acetophenone | 3.5 | 85.3 | 110 (30) | $C_{10}H_{12}O_2$ | — | — | — | — |
| Methyl benzyl ketone | 1.5 | 78.5 | 133–134 (40) | $C_{11}H_{14}O_2$ | 1.0520[a] | 1.51028[a] | 50.49 | 50.62 |
| Dibenzyl ketone[f] | 1.15 | 85.8 | 200–202 (18) | $C_{12}H_{18}O_2$[i] | — | — | — | — |
| Benzophenone | 5.0 | 81.4 | 168 (10) | $C_{15}H_{14}O_2$ | 1.1794[a] | 1.59013[a] | 65.36 | 65.53 |

[a] Temperature, 19.5°C. [b] E. J. Salmi and P. Louhenkurru, *Chem. Ber.* **72**, 600 (1939) give $d_4^{20}$ 1.1116; $n_D^{20}$ 1.52513. [c] The bromine addition product, b.p. 80–90°C (30 mm Hg), was a purple liquid which gradually split off hydrobromic acid, upon standing. [d] Temperature, 21°C. [e] E. J. Salmi, *Chem. Ber.* **71**, 1803 (1938) gives $d_4^{20}$ 1.0280; $n_D^{20}$ 1.45828. [f] The acetal crystallized: m.p. 69°C (from methanol). [g] Data by E. J. Salmi and K. Kyriki, *Suomen Kemistilehti* **19B**, 97 (1946). [h] Data by E. J. Salmi and V. Rannikko, *Chem. Ber.* **72**, 600 (1939). [i] This formula is wrong and should be $C_{17}H_{18}O_2$. The melting point also appears to be different than that reported by V. A. Stoute and M. A. Winnik (1975), *Can. J. Chem.* **53** (23) 3503 who report a m.p. of 36–37°C for 2,2-dibenzyl-1,3-dioxolane (dibenzyl ketone ethylene ketal) in 85% yield. These latter authors also report the boiling point for the ethylene glycol ketal of methyl benzyl ketone (phenyl acetone) of 90°C at 0.2 Torr (75% yield). [Adapted from M. Sulzbacher, E. Bergmann, and E. R. Pariser, *J. Amer. Chem. Soc.* **70**, 2827 (1948). Copyright 1948 by the American Chemical Society. Reprinted by permission of the copyright owner.]

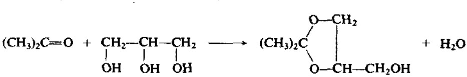
The reaction of glycerol with formaldehyde and other aldehydes to give 1,2- and 1,3-condensation products has been recently reviewed (Eq. 17) [17a]. The structures of the four isomeric acetals obtained by the reaction of glycerol with *n*-hexadecanol have been reported [17b].



(17)

Ketones react with glycerol to give mainly the 1,2-disubstituted product, as is illustrated in Preparation 2-4, using acetone.

***2-4. Preparation of (RS)-1,2-Isopropylideneglycerol* [18]**

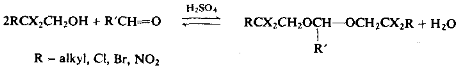


(18)

To a three-necked flask fitted with a mechanical stirrer, Dean-Stark trap, and condenser is added 237 gm (300 ml, 4.90 moles) of acetone, 100 gm (1.09 mole) of dry glycerol, 300 ml of petroleum ether (b.p. 35–55°C), and 3.0 gm of *p*-toluenesulfonic acid. The contents are refluxed until 19.6 ml of water separates (approx. 21–36 hr), then 3.0 gm of sodium acetate is added, and the contents stirred for $\frac{1}{2}$ hr, filtered, concentrated and the residue distilled to afford 125–129 g (94–98%), b.p. 80–81°C (11 mm Hg), $n_D^{25}$ 1.4339, $d_4^{25}$ 1.062.

The aldehydes or ketals used may have other substituents present, such as olefinic [19], halo [20a–d], amino [20c, 21], nitro [22a,b], and carbethoxy [20c, 23] groups as long as they do not interfere with the acetalization or ketalization reaction [19].

With negatively substituted alcohols, acetal formation is difficult to achieve by the normal synthetic methods. Ship and Hill have reported good yields for the formals of 2,2,2-tribromoethanol, 2,2,2-trinitroethanol, and 2,2-dinitropropanol by reaction with formaldehyde (paraformaldehyde) in concentrated sulfuric acid (Eq. 19) [24a].



$$2RCX_2CH_2OH + R'CH{=}O \overset{H_2SO_4}{\rightleftharpoons} RCX_2CH_2O\underset{R'}{\underset{|}{C}}H{-}OCH_2CX_2R + H_2O \quad (19)$$

R = alkyl, Cl, Br, $NO_2$
R′ = H, $CCl_3$, or CH=O
X = Cl, Br, $NO_2$

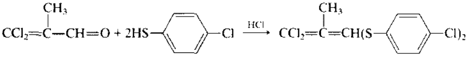
Negatively substituted diols produce the corresponding dioxanes with formaldehyde, chloral, and glyoxal. Surprisingly, aliphatic alcohols such as propanol, 2,2-dimethyl-1-propanol, and 1,3-propanediol, which do not have negative substitutions, are unreactive [24a]. Some examples illustrating this method are shown in Table IV.

### 2-5. *Preparation of Di-*t*-Butylmercaptal of Formaldehyde* [24b]

$$2(CH_3)_3C{-}SH + CH_2{=}O(\textit{para}) \xrightarrow{\text{HCl gas}} [(CH_3)_3CS]_2CH_2 + H_2O \qquad (20)$$

To a flask is added 180 g (2.0 mole) of *t*-butyl mercaptan and 30 g (1.0 mole) of paraformaldehyde. Hydrogen chloride gas was bubbled through the mixture of 3 hr while maintaining the temperature at 25–30°C. At the end of this time, two layers formed, and the lower aqueous layer was removed. The organic layer was then extracted with hexane, washed with water, dried and concentrated to remove hexane. The residue was distilled to give 170 g of product, $n_D^{22}$ 1.4903.

### 2-6. *Preparation of 3,3-Dichloro-2-Methacrolein bis(4-chlorophenyl) mercaptal* [24c]



(21)

To a flask is added 25.8 g (0.185 mole) of 3,3-dichloro-2-meth-acrolein, 58.0 g (0.40 mole) of 4-chlorothiophenol, and 300 ml petroleum ether (b.p. 85–95°C). Then anhydrous hydrogen chloride gas is bubbled through the solution for a period of 3 hr while the temperature is raised to 76°C. The mixture is cooled and the precipitated product is filtered. The product is isolated in 60 g (75% yield).

Analysis: Calculated, Cl, 34.6; S, 15.6;
Actual, Cl, 34.0; S, 15.5

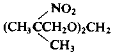
## B. Reactions of Alcohols with Vinyl Ethers

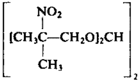
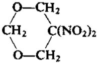
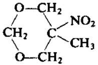
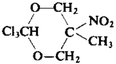
In the presence of catalysts, methyl vinyl ether reacts with alcohols, thiols, and ortho esters to give acetals as shown in Scheme 3. In the case of methyl vinyl ether or the other alkyl vinyl ethers, the yields of acetal are usually only fair. In some cases the yields are very good.

Ethyl vinyl ether reacts in similar manner to give acetals, and a typical procedure is illustrated in Preparation 2-5. Some other examples in which a

## TABLE IV

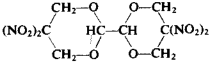
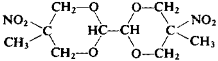
### ACETAL PREPARATION IN SULFURIC ACID[a]

| Alcohol | Aldehyde[k] | Product | B.p., °C (mm Hg) or m.p., °C | Initial $H_2SO_4$ concn. (%) | Moles of alcohol per liter of acid[b] | Yield (%) | Method of purification |
|---|---|---|---|---|---|---|---|
| 2,2,2-Tribromoethanol | F | Bis(2,2,2-tribromoethyl) formal<br>$(CBr_3CH_2O)_2CH_2$ | 71–72 | 96.4 | 4.0 | 10 | Recrystallization from pentane |
| | | | | 89.6 | 4.0 | 78 | |
| | | | | 89.6 | 2.0 | 74 | |
| | | | | 89.6 | 0.5 | 13 | |
| | | | | 85.2 | 2.0 | 80 | |
| | | | | 80.0 | 0.5[c] | 63 | |
| | | | | 70.0 | 0.5[d] | 5 | |
| 2,2,2-Trichloroethanol | F | Bis(2,2,2-trichloroethyl) formal[d]<br>$(CCl_3CH_2O)_2CH_2$ | 12.5<br>87 (1) | 90 | 12 | 70 | Distillation under reduced pressure |
| 2,2,2-Trifluoroethanol | F | Bis(2,2,2-trifluoroethyl) formal[d]<br>$(CF_3CH_2O)_2CH_2$ | −28<br>31 (25) | 96.4 | 12 | 68 | Distillation under reduced pressure |
| 2,2,2,3-Tetrafluoropropanol | F | Bis(2,2,3,3-tetrafluoropropyl) formal[d]<br>$(HCF_2CF_2CH_2O)_2CH_2$ | 57–58<br>(5.5) | 90 | 12 | 63.4 | Distillation under reduced pressure |
| 2-Methyl-2-nitropropanol | F | Bis(2-methyl-2-nitropropyl) formal[d]<br> $(CH_3\overset{NO_2}{\underset{CH_3}{C}}CH_2O)_2CH_2$ | 65–66 | 90 | 4 | 0 | Recrystallization from 70% $CH_3OH–H_2O$ |
| | | | | 90 | 8 | 10 | |
| | | | | 90 | 12 | 45 | |
| | | | | 90 | 12[e] | 60 | |
| | | | | 90 | 12[f] | 78 | |
| | | | | 96 | 12 | 0.4 | |
| 2,2-Dinitropropanol | F | Bis(2,2-dinitropropyl) formal<br>$[CH_3C(NO_2)_2CH_2O]_2CH_2$ | 33–33.5 | 96.4 | 12 | 70 | Recrystallization from 75% $CH_3OH–H_2O$ |
| | | | | 96.4 | 8 | 33 | |
| | | | | 96.4 | 4 | 0 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 2,2,2-Trinitroethanol | F | Bis(2,2,2-trinitroethyl) formal<br>$[(NO_2)_3CCH_2O]_2CH_2$ | 64–65 | 96 | 4 | 90 | Recrystallization from 50% MeOH–$H_2O$ |
| 2-Methyl-2-nitropropanol | G | Tetra(2-methyl-2-nitropropyl) glyoxal acetal | 189–191 | 90 | 8 | 35 | Recrystallization from 70% γ-butyrolactone–$H_2O$ |
| 2-Methyl-2-nitropropanol | F | <br>$\left[[CH_3\overset{NO_2}{\underset{CH_3}{C}}—CH_2O]_2CH\right]_2$ | | | | | |
| 2,2-Dinitro-1,3-propanediol | | 5,5-Dinitro-1,3-dioxane<br> | 53[g] | 96 | 4 | 69 | Recrystallization from γ-butyrolactone–$H_2O$ |
| 2-Methyl-2-nitro-3-propanediol | F | 5-Methyl-5-nitro-1,3-dioxane[c,h]<br> | 71[i] | 90<br>96<br>96 | 4<br>4<br>8 | 70<br>68<br>75 | Recrystallization from 50% $CH_3OH$–$H_2O$ |
| 2-Methyl-2-nitro-1,3-propanediol | C | 2-Trichloromethyl-5-methyl-5-nitro-1,3-dioxane[c]<br> | 195–196 | 90<br>96 | 1<br>2 | 35<br>71 | Recrystallization from 70% $CH_3OH$–$H_2O$ |

(*continues*)

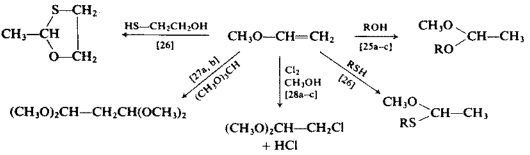
TABLE IV (*Continued*)

| Alcohol | Aldehyde[k] | Product | B.p., °C (mm Hg) or m.p., °C | Initial $H_2SO_4$ concn. (%) | Moles of alcohol/ per liter of acid | Yield (%) | Method of purification |
|---|---|---|---|---|---|---|---|
| 2,2-Dinitro-1,3-propanediol | G | 2,6,2′,6′-Tetraoxa-4,4,4′,4′-tetranitrobicyclohexyl[j]<br> | 259–260 (dec.) | 96 | 1 | 59 | Recrystallization from 80% γ-butyrolactone–$H_2O$ |
| 2-Methyl-2-nitro-1,3-propanediol | G | 2,6,2′,6′-Tetraoxa-4,4′-dimethyl-4,4′-dinitrobicyclohexyl<br> | >300 | 90 | 4 | 34 | Recrystallization from 80% γ-butyrolactone–$H_2O$ |

[a] Reaction at room temperature of stoichiometric amounts of alcohol and aldehyde unless otherwise noted. [b] The percentages given for acid concentrations are for initial acid strength since water which forms in the reaction decreases the acidity, e.g., in the reaction of 0.06 mole of 2,2,2-tribromoethanol in 5 ml of 96% sulfuric acid, 0.5 gm of water is formed by complete reaction of the alcohol with formaldehyde, reducing the acid strength to 90% in the final reaction mixture. [c] Saturated solution of alcohol. [d] Initial reaction temperature of 0° with reverse addition of reactants. [e] Alcohol to aldehyde ratio = 1:1. [f] Alcohol to aldehyde ratio = 4:1 and yield is based on aldehyde. [g] M. H. Gold, E. E. Hamel, and K. Klager, *J. Org. Chem.* **22**, 1665 (1957). [h] Product did not precipitate from acid medium. [i] M. Senkus, *J. Amer. Chem. Soc.* **63**, 2635 (1940). [j] Glyoxal bisulfite was used. [k] F, Formaldehyde; G, glyoxal; C, chloral. [Reprinted in part from K. G. Shipp, and M. E. Hill, *J. Org. Chem.* **31**, 853 (1966). Copyright 1966 by the American Chemical Society. Reprinted by permission of the copyright owner.]

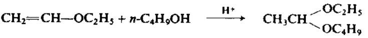
SCHEME 3

Reactions of Methyl Vinyl Ether to Give Acetals



variety of alkyl vinyl ethers react with alcohols to give acetals or ketals are shown in Table V.

### *2-7. Preparation of 1-*n*-Butoxy-1-ethoxyethane* [25b]



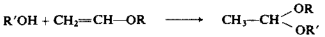
$$CH_2{=}CH{-}OC_2H_5 + n\text{-}C_4H_9OH \xrightarrow{H^+} CH_3CH\begin{cases} OC_2H_5 \\ OC_4H_9 \end{cases} \qquad (22)$$

To a flask containing 74 gm (1.0 mole) of *n*-butanol and 1.0 gm of conc. sulfuric acid is slowly added, with stirring, 72 gm (1.0 mole) of ethyl vinyl ether at a temperature not exceeding 30°C. The reaction mixture is stirred for 3–4 hr after the addition, potassium carbonate is added to destroy the acid catalyst, and then the mixture is distilled to afford 88.0 gm (60%), b.p. 151–152°C.

The use of a less active catalyst such as glacial acetic acid necessitates that the reaction be carried out at higher temperatures and under pressure [25b].

The same product may also be obtained by the reaction of ethanol with *n*-butyl vinyl ether [25b].

In general, alcohols and phenols react under anhydrous conditions with alkyl vinyl ethers in the presence of hydrogen halides [25a,b, 29a–c] or sulfonated styrene resin [30] to afford acetals (Eq. 23). The acid catalyst is



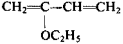
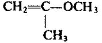
$$R'OH + CH_2{=}CH{-}OR \longrightarrow CH_3{-}CH\begin{cases} OR \\ OR' \end{cases} \qquad (23)$$

neutralized before distillation to recover the acetal. The use of high-boiling alcohols can also remove the original alkyl ether group to give symmetrical acetals [30]. For example: R′ = 2-methylhex-3-yn-5-ene-2-ol [29a], ethylene chlorohydrin [31], methylbutynol [31], propyne semiacetal of chloral [31], trialkylsilanols [31], polyvinyl alcohol [31], trimethylolethane [32], nitro alcohols [33], sucrose [34], phenol [35, 36], glycerol

## TABLE V

### Reaction of Alkyl Vinyl Ethers with Various Reagents to Give Acetals or Ketals

| $ROCH{=}CH_2$ (moles) R = | Reagent (moles) | Solvent (ml) | Catalyst (gm) | Reaction conditions Temp. (°C) | Reaction conditions Time (hr) | Yield (%) | B.p., °C (mm Hg) | $n_D$ (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| $C_2H_5$ (1.0) | $n$-$C_4H_9OH$ (1.0) | — | $H_2SO_4$ (1.0) | 30 | 5 | 60 | 151–152 (760) | — | *a* |
| $C_2H_5$ (1.1) | $C_6H_5OH$ (0.96) | Ether 50 | $C_2H_5OCHClCH_3$ (2.0) | 15 | 1–2 | 80–85 | 83–84 (10.5) | — | *a* |
| $C_2H_5$ (1.05) | $Cl—CH_2CH_2OH$ (1.0) | 50 | $SOCl_2$ (0.5) | 15 | 1–2 | 50 | 53–56 (10) | — | *a* |
| $C_2H_5$ (2.0) | $\underset{OH}{CH_2}—\underset{OH}{CH_2}$ (1.0) | 50 | $C_2H_5OCHClCH_3$ (4) | 15 | 1–2 | 50 | 97 (13) | — | *a* |
| $C_2H_5$ (0.070) | Cholesterol (0.031) | 5 | (0.4) | 15 | 1 | — | — | — | *a* |
| $CH_3$ (3.0) | $CH_3OH$ (20.0)<br>$Br_2$ (3.0) | — | — | −50 | 1–2 | 50 | 56–62 (30) | — | *b* |
| $CH_3$ (2.0) | $CH(SC_2H_5)_3$ (4.0) | — | $BF_3 \cdot O(C_2H_5)_2$ (0.25) | 30 | 2 | 57 | 122–131 (3) | 1.5178 (25) | *c* |
| $CH_3$ (2.0) | $C_2H_5SH$ (2.0) | 120 | $C_2H_5OCHClCH_3$ (2) | 0–5 | 1.5–2.0 | 87 gm<br>46 gm | 130–132[d]<br>77 (13)[e] | — | *f* |
| $CH_3$ (2.7) | $CH(OCH_3)_3$ (6.0) | — | $BF_3 \cdot O(C_2H_5)_2$ (2.25) | 25–41 | 1–2 | 85 | 66–67 (12) | 1.4052 (25) | *g* |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| $CH_3$<br>(1.1) | $CH_3CH(OCH_3)_2$<br>(1.2) | — | $SnCl_4$<br>(1.2) | 20–45 | 5 | — | 73–80<br>(24) | — | *g* |
| $C_2H_5$<br>(1.0) | *n*-$C_4H_9OH$<br>(1.0) | — | Styrene sulfone resin IR-120 (75) | 100 | 4 | 13 | 184–186<br>(760) | 1.4100<br>(16) | *h* |
| (1.0) | *n*-$C_7H_{15}OH$<br>(0.95) | — | (75) | 100 | 4 | 28 | 152–154<br>(15) | 1.4320<br>(18) | *h* |
| (0.42) | *n*-$C_{12}H_{25}OH$<br>(0.33) | $\frac{C_6H_6}{100}$ | (30) | 40 | 1–2<br>Sealed tube | 40 | 288<br>(15) | 1.4420<br>(18) | *h* |
|  $CH_2{=}C(OC_2H_5){-}CH{=}CH_2$<br>(0.15) | $C_2H_5OH$<br>(0.15) | — | — | 100 | 24 | 28 | 72–75<br>(9) | 1.4148<br>(20) | *i* |
|  $CH_2{=}C(CH_3){-}OCH_3$<br>(0.83) | *i*-$C_3H_7OH$<br>(2.0) | — | *p*-Toluene sulfonic acid<br>(0.035) | 20 | ½ | 21[k] | | | *j* |
| | | | | | | 42[l] | 45 (59) | 1.3876<br>(25) | |
| | | | | | | 23[m] | — | 1.3977<br>(25) | |

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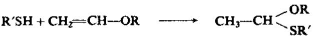
[a] W. Reppe and K. Baur, U.S. Pat. 2,000,252 (1935). [b] O. W. Cass, U.S. Pat. 2,433,890 (1948). [c] J. W. Copenhaver, U.S. Pat. 2,500,486 (1950). [d] Methyl ethyl thiol acetal. [e] Diethyl mercaptal. [f] J. W. Copenhaver, U.S. Pat. 2,551,421 (1951). [g] J. W. Copenhaver, U.S. Pat. 2,527,533 (1950). [h] P. Mastagli, P. Lambert, and G. Francois, *Bull. Soc. Chim. France* 764 (1957). [i] H. B. Dykstra, *J. Amer. Chem. Soc.* **57**, 2255 (1935). [j] W. L. Howard and N. B. Lorette, *J. Org. Chem.* **25**, 525 (1960). [k] Acetone dimethyl ketal. [l] Acetone isopropyl methyl ketal. [m] Acetonediisopropyl ketal.

[36], pentaerythritol [36], and glycols [37]; R = alkyl, for example, methyl, ethyl, dodecyl [38], tridecyl [38], heptadecyl [38].

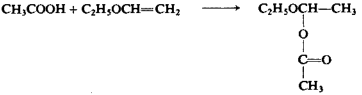
Mercaptans also react with vinyl ethers, forming thioacetals (Eq. 24) [39].



$$R'SH + CH_2{=}CH{-}OR \longrightarrow CH_3{-}CH\begin{matrix}OR\\SR'\end{matrix} \qquad (24)$$

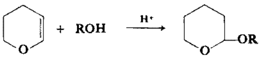
The use of excess mercaptan, under the appropriate conditions, affords mercaptals. For example, methyl vinyl ether reacts with ethyl mercaptan to afford diethyl mercaptal [bp 77°C (13 mm Hg)]. Hydrogen sulfide adds to vinyl butyl ether to give anti-Markovnikov addition to afford 2-butoxyethyl mercaptan and sulfide [40].

Carboxylic acids add in a similar manner to afford acetal acylals (Eq. 25) [25b, 41].



$$CH_3COOH + C_2H_5OCH{=}CH_2 \longrightarrow C_2H_5O\underset{\begin{array}{c}|\\O\\|\\C{=}O\\|\\CH_3\end{array}}{CH}{-}CH_3 \qquad (25)$$

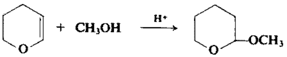
Cyclic vinyl ethers such as dihydropyran react with aliphatic and aromatic hydroxy compounds to give cyclic acetals in good yields, as shown in Eq. 26 [42a,b]. Hydrochloric acid catalyzes the room temperature reaction, which is complete in about 3 hr. Several examples of this reaction are shown in Table VI and are illustrated in Preparation 2-6.



(26)

Recently starch acetals have also been prepared by this method wherein starch was reacted with dihydropyran (3,4-dihydro-2*H*-pyran) in the presence of catalytic amounts of 25% hydrochloric acid at room temperature [43].

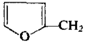
***2-8. Preparation of 2-Methoxytetrahydropyran* [42a]**



(27)

TABLE VI

PREPARATION OF ACETALS FROM DIHYDROPYRAN

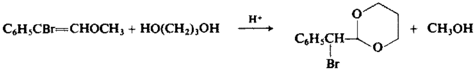
| ROH, R= | Yield (%) | B.p., °C (mm Hg) or m.p., °C | $n_D^{20}$ | Ref. |
|---|---|---|---|---|
| $CH_3$ | 85 | 125 (760) | 1.4260 | a |
| $C_2H_5$ | 93 | 146 (760) | 1.4248 | a |
| $BrCH_2CH_2$ | 82 | 94 (14) | 1.4810 | b |
| $n$-$C_3H_7$ | 91 | 165 (760) | 1.4280 | a |
| $ClCH_2CH_2CH_2$ | 78 | 103 (14) | 1.4515 | b |
| $C_2H_5OCH_2CH_2CH_2$ | 60 | 93 (10) | 1.4364 | b |
| $CH_2{=}CHCH_2$ | 70 | 126 (760) | 1.4440 | a |
| $n$-$C_4H_9$ | 75 | 183 (760) | 1.4312 | a |
| $HOCH_2(CH_2)_4$ | 39 | 120 (3) | 1.4599 | b |
| $-(CH_2)_5$ | 20 | 149 (2) | 1.4638 | b |
|  | 34 | 124 (24) | 1.4828 | a |
| $C_6H_5$ | 77 | 103 (4) | 1.5228 | a, b |
| $p$-$BrC_6H_4$ | 83 | 109 (0.26)<br>57–57.5 | — | b |
| $p$-$NO_2$—$C_6H_4$ | — | 59–60 | — | c |
| $C_6H_5CH_2$ | 41 | 107 (3) | 1.5728 | b |
| $o$-$C_6H_4$< | 55 | 170 (0.65) | 1.5238 | b |
| $m$-$C_6H_4$< | 86 | 197 (4) | 1.5340 | b |
| $p$-$C_6H_4$< | 54 | 125–127 | — | b |

[a] G. F. Woods and D. N. Kramer, *J. Amer. Chem. Soc.* **69**, 2246 (1947). [b] W. E. Parham and E. L. Anderson, *J. Amer. Chem. Soc.* **70**, 4187 (1948). [c] T. H. Fife and L. K. Jao, *J. Amer. Chem. Soc.* **90**, 4081 (1968).

To a flask equipped with a stirrer and containing 84.0 gm (1.0 mole) of 2,3-dihydropyran in the presence of 1 ml of conc. hydrochloric acid is added 32.0 gm (1.0 mole) of methanol. The reaction is exothermic and is stirred for 3 hr. Then a few pellets of sodium hydroxide are added to make the reaction basic. The mixture is directly distilled to afford 98.6 gm (85%), b.p. 125°C (760 mm Hg), $n_D^{20}$ 1.4260.

Polysubstituted vinyl ethers also condense with alcohols to give acetals. For example, bromomethoxystyrene reacts with 1,3-propanediol (trimethylene glycol) to afford the cyclic acetal 2-(α-bromobenzyl)-1,3-dioxolane described in Preparation 2-7.

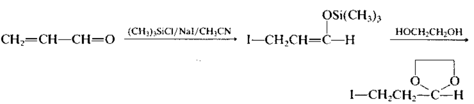
### *2-9. Preparation of 2-(α-Bromobenzyl)-1,3-dioxolane* [44a]



(28)

To a flask containing a solution of 5.0 gm (0.023 mole) of α-bromo-β-methoxystyrene, 10.0 gm (0.11 mole) of 1,3-propanediol and 10 ml of dioxane is added 3 drops of conc. sulfuric acid. The reaction mixture is stirred well and allowed to stand at room temperature for 10 days. Then dilute sodium carbonate solution is added to neutralize the acid. Water and dioxane are removed under reduced pressure on the steam bath, the residue dissolved in 50 ml of ether, dried, concentrated, and distilled under reduced pressure to afford 2.8 gm (47%), b.p. 120–125°C (1.0 mm Hg), m.p. 46–47°C (from 50% ethanol).

Recently it has been reported that enol silyl ethers prepared from α,β-unsaturated aldehydes and ketones can be reacted with ethylene glycol to give 1,3-dioxolanes. This has been illustrated for the preparation of 2-(2-iodoethyl)-1,3-dioxolane (44b) as shown in Eq. (29).



(29)

## C. Reaction of Alcohols with Olefins and Acetylenes

a. OLEFINS

Simple olefins including many monosubstituted and 1,2-disubstituted ethylenes are catalytically oxidized by alcoholic solutions of $PdCl_2$ or $PdCl_2$-$CuCl_2$-oxygen to afford the corresponding acetals or ketals (45a). The presence of $CuCl_2$ and molecular oxygen helps to convert any free palladium metal to $PdCl_2$ (Eqs. 30–32).

$$CH_2{=}CH_2 + 2ROH + PdCl_2 \longrightarrow CH_3CH(OR)_2 + 2HCl + Pd^{\circ} \qquad (30)$$

$$Pd^{\circ} + 2CuCl_2 \longrightarrow PdCl_2 + Cu_2Cl_2 \qquad (31)$$

$$Cu_2Cl_2 + 2HCl + \tfrac{1}{2}O_2 \longrightarrow 2CuCl_2 + H_2O \qquad (32)$$

## TABLE VII

### OXIDATIONS OF SOME OLEFINS WITH ALCOHOLIC Pd(II) SALTS

| Olefin | Alcohol | Catalyst | Conditions | Products | Yield[a] (%) |
|---|---|---|---|---|---|
| Ethylene | Ethanediol | *b* | *c* | 2-Methyl-1,3-dioxolane | 91 |
| | | | | Acetaldehyde | 9 |
| Ethylene | 1,3-Propanediol | *b* | *c* | 2-Methyl-1,3-dioxane | High |
| 1-Butene | Ethanediol (wet) | *d* | *c* | 2-Ethyl-2-methyl-1,3-dioxolane | 68 |
| | | | | 2-Butanone | 30 |
| 1-Hexene | 1-Propanol | *e* | *f* | 2-Hexanone | 75 |
| | | | | 3-Hexanone | 25 |
| 1-Octene | 1-Propanol | *e* | *g* | Octanones | 89[h] |
| | | | | 2-Octanone | 87 |
| | | | | 3-Octanone | 1.5 |
| | | | | 4-Octanone | Trace |
| 1-Octene | 1-Propanol | *e* | *i* | Octanones | 80[h] |
| | | | | 2-Octanone | 68 |
| | | | | 3-Octanone | 9 |
| | | | | 4-Octanone | 3 |
| 1-Octene | 1-Propanol | *e* | *j* | Octanones | 73[h] |
| | | | | 2-Octanone | 45 |
| | | | | 3-Octanone | 18 |
| | | | | 4-Octanone | 10 |
| Cyclohexene | Ethanol | *k* | *j* | Cyclohexanone | 95 |
| Cyclohexene | Ethanediol | *k* | *f* | 1,4-Dioxospiro[4.5]decane | High |
| *trans*-3-Hexene | 1-Propanol | *l* | *f* | 3-Hexanone | 84 |
| | | | | 2-Hexanone | 14 |
| *cis*-2-Butene | Methanol | *d* | *m* | Butanone | 99$^+$ |
| *trans*-2-Butene | Methanol | *d* | *m* | Butanone | 99$^+$ |
| 2,5-Dihydrofuran | Ethanol | *l* | *f* | 3,3-Diethoxytetrahydrofuran | 94 |
| 2,5-Dihydrofuran | Ethanol | *n* | *f* | 3,3-Diethoxytetrahydrofuran | 86 |
| Acrylonitrile | Ethanediol | *e* | *o* | 1,3-Dioxolane-2-acetonitrile | High |
| Acrylonitrile | Methanol | *e* | *p* | 2,2-Dimethoxypropionitrile | High |
| 1-Hexene | Glycerol | *e* | *q* | 2-*n*-Butyl-2-methyl-1,3-dioxolane-4-methanol | 70 |
| | | | | Hexanone | 26 |

[a] Based upon integrated areas of gas chromatograms. [b] 0.028 *M* $PdCl_2$, 0.586 *M* $CuCl_2 \cdot 2H_2O$. [c] 40 min at 50°C in autoclave under initially 100 psi oxygen. [d] 0.028 *M* $PdCl_2$, 0.141 *M* $CuCl_2 \cdot 2H_2O$. [e] 0.020 *M* $PdCl_2$, 0.100 *M* $CuCl_2 \cdot 2H_2O$. [f] 120 min at 50°C and 3 atm oxygen. [g] 120 min at 30°C and 3 atm oxygen. [h] Using technical grade 1-octene. [i] 120 min at 60°C and 3 atm oxygen. [j] 120 min at 90°C and 3 atm oxygen. [k] 0.028 *M* $PdCl_2$, 0.117 *M* $CuCl_2 \cdot 2H_2O$. [l] 0.020 *M* $PdCl_2$, 0.100 *M* $CuCl_2$. [m] 45 min at 50°C under initially 100 psi oxygen. [n] 0.020 *M* $PdCl_2$ 0.100 *M* $Cu(NO_3)_2$. [o] 180 min at 80°C under 3 atm oxygen. [p] 180 min at 75°–85°C under 3 atm oxygen. [q] Combined with an equal volume of methanol to make system completely homogeneous, then allowed to react for 120 min at 50°C and 3 atm oxygen. [Reprinted from W. G. Lloyd and B. J. Luberoff, *J. Org. Chem.* **34**, 3949 (1969). Copyright 1969 by The American Chemical Society. Reprinted by permission of the copyright owner.]

TABLE VIII

PREPARATIVE DATA AND PHYSICAL CONSTANTS OF ACETALS[a] FROM THE REACTION OF ACETYLENE WITH ALCOHOLS

| Starting alcohol | Taken (gm) | Product | | | | |
|---|---|---|---|---|---|---|
| | | Yield (gm) | Yield (%) | B.p., °C (mm Hg) | $d_4$ | $n_D$ |
| Methyl alcohol | 200 | 104 | 37 | 64–65 | $0.8494^{26}$ | $1.3762^{26}$ |
| Ethyl alcohol | 200 | 104 | 40 | 101–102 | $0.8250^{23}$ | $1.3789^{30}$ |
| Propyl alcohol | 203 | 90 | 37 | 146–148.5 | $0.8256^{26}$ | $1.3938^{26}$ |
| Isopropyl alcohol | 200 | 97 | 40 | 82–84 | $0.7855^{25}$ | $1.3790^{25}$ |
| Butyl alcohol | 100 | 39.5 | 33.6 | 197–198 | $0.8312^{26}$ | $1.4090^{26}$ |
| *n-sec*-Butyl alcohol | 33 | 14 | 35 | 55–60 (16) | — | $1.3965^{29}$ |
| Primary isobutyl alcohol | 200 | 102 | 43.4 | 168–169 | $0.8123^{24}$ | $1.4037^{24}$ |
| *n*-Amyl alcohol | 200 | 117 | 51.5 | 114–116 (16) | $0.8282^{26}$ | $1.4159^{26}$ |
| Isobutyl carbinol | 200 | 117 | 51.5 | 210–211 | $0.8278^{23}$ | $1.4175^{23}$ |
| *sec*-Butyl carbinol | 200 | 100 | 43.6 | 205–206 | $0.8262^{25}$ | $1.4165^{25}$ |
| Methylpropyl carbinol | 130 | 45 | 30 | 120–123 | $0.8128^{24}$ | $1.4069^{24}$ |
| Methylisopropyl carbinol | 59 | 21 | 30 | 142–145 | — | $1.4095^{27}$ |
| Diethyl carbinol | 78 | 36 | 40 | 120–121 | $0.8120^{27}$ | $1.4050^{27}$ |
| Dimethyl ethyl carbinol | 200 | 123 | 53.7 | 90–93 | $0.8278^{26}$ | $1.3965^{26}$ |
| Diethyl methyl carbinol | — | — | — | 96–99 | — | $1.3872^{23}$ |
| Triethyl carbinol | — | — | — | 114–116 | — | $1.4135^{26}$ |
| Methylethyl butyl carbinol | — | — | — | 125–128 | — | $1.4145^{25}$ |
| Allyl alcohol | — | — | — | 90–93 (16) | — | $1.4351^{28}$ |
| Tetrahydrofurfuryl alcohol | 104 | 37 | 31.6 | 153–155 (18) | $1.3700^{27}$ | $1.4563^{26}$ |
| Cyclohexanol | — | — | — | 131–134 (16) | $0.9560^{25}$ | $1.4651^{25}$ |
| Benzyl alcohol | 200 | 102 | 45.5 | 187–189 (16) | $1.0455^{25}$ | $1.5397^{25}$ |
| Diphenyl carbinol | — | — | — | 201–202 (18) | — | $1.5545^{25}$ |
| Phenyl ethyl alcohol | 122 | 68 | 50.4 | 204–205 (16) | $1.0180^{26}$ | $1.5302^{26}$ |
| Phenyl methyl carbinol | — | — | — | 164–166 (17) | — | $1.5365^{25}$ |
| Phenyl ethyl carbinol | 70 | 31 | 40 | 185–187 (16) | — | $1.5495^{25}$ |
| Phenyl methyl ethyl carbinol | — | — | — | 200 (14) | — | $1.5801^{25}$ |

[a] The conditions for this reaction are similar to those described in Table X. [Reprinted from H. D. Hinton and J. A. Nieuwland, *J. Amer. Chem. Soc.* **52,** 2892 (1930). Copyright 1930 by The American Chemical Society. Reprinted by permission of the copyright owner.]

Terminal olefins, as shown in Eq. (23), are mainly converted to the corresponding methyl ketones or ketals. Palladium chloride also catalyzes the oxidation and isomerization of higher α-olefins. For example, 1-hexene and 1-octene afford mixtures of 2- and 3-hexanones and *n*-octanones, respectively.

$$\text{RCH}{=}\text{CH}_2 + 2\text{ROH} \xrightarrow{\text{PdCl}_2} \text{R—C(OR)}_2\text{—CH}_3 + \text{H}_2\text{O} \qquad (33)$$

1,2-Disubstituted ethylenes oxidize to the ketone or ketal. Anhydrous conditions favor ketal formation.

Some examples indicating the scope of method are shown in Table VI.

Some monosubstituted ethylenes undergo solvolysis rather than oxidation. For example, ethyl vinyl ether affords acetal, vinyl acetate affords ethyl acetate and acetal, and vinyl chloride affords mainly acetal with a little chloro acetal.

Based on these limitations, the use of simple olefins to give acetals or ketals is rather restricted. The preceding method needs further investigation in order to demonstrate its preparative value.

### b. ACETYLENES

Acetylene reacts with alcohols in the presence of boron trifluoride and mercuric oxide to afford acetals [46a,b]. Substituted acetylenes react with alcohols to give ketals [47a–d]. The reaction probably proceeds via the intermediate vinyl ether as shown in Eq. (34) [48].

$$\text{ROH} + \text{HC}{\equiv}\text{CH} \xrightarrow{\text{HgO—BF}_3} \text{ROCH}{=}\text{CH}_2 \xrightarrow{\text{ROH}} (\text{RO})_2\text{CH—CH}_3 \qquad (34)$$

Some examples illustrating the utility of this reaction are shown in Table IX and in Preparation 2-8.

The reaction of vinyl ethers with alcohols to give acetals is also described in detail in Section 2B of this chapter.

Monohydric alcohols other than methanol react with monoalkylacetylenes to afford polymers [47d]. However, the use of trichloroacetic acid causes the reaction to proceed smoothly to 2,2-dialkoxyalkanes [47d].

The reaction of alcohols with conjugated vinylacetylene in the presence of $CCl_3COOH$ catalyst gives $\beta$-alkoxy ketals [49]. The use of only sodium methoxide as the catalyst causes the addition of only 1 mole of methanol to vinylacetylene at 100°C to give 4-methoxy-1-butyne. The use of $HgO{-}BF_3$ causes the addition of 3 moles of methanol to give 1,3,3-trimethoxybutane [50].

### *2-10. Preparation of 1,1-Dimethoxyethane* [46a,b]

$$2\text{CH}_3\text{OH} + \text{HC}{\equiv}\text{CH} \longrightarrow (\text{CH}_3\text{O})_2\text{CH—CH}_3 \qquad (35)$$

To a flask equipped with a mechanical stirrer, condenser, and gas addition tube and containing 10 gm of a 63% solution of boron trifluoride in methanol is added 1.0 gm of mercuric oxide and 200 gm (6.25 moles) of methanol. Then 70 gm (3.13 moles) of acetylene is added with vigorous stirring at room temperature. After the reaction the catalyst is neutralized

## TABLE IX

### PREPARATIVE DATA AND PHYSICAL CONSTANTS OF CYCLIC ACETALS[a] FROM THE REACTION OF ACETYLENE WITH ALCOHOLS (STOICHIOMETRIC QUANTITIES)

| Starting alcohol | Taken (gm) | Yield (gm) | Yield (%) | B.p., °C (mm) | $d_4$ | $n_D$ |
|---|---|---|---|---|---|---|
| Ethylene glycol | 102 | 88 | 62 | 82.3 | $0.9770^{24}$ | $1.3945^{24}$ |
| Trimethylene glycol | 93 | 55 | 45 | 108–111 | $0.9675^{23}$ | $1.4160^{23}$ |
| Pinacol | — | — | — | 133–134 | — | — |
| Methylethyl pinacol | — | — | — | 150–180 | — | — |
| Glycol methyl ether | 150 | 77 | 44 | 87–91 (15) | $0.9691^{25}$ | $1.4181^{25}$ |
| Glycol ethyl ether | 300 | 255 | 74 | 110–114 (14) | $0.9328^{25}$ | $1.4163^{25}$ |
| Glycol butyl ether | 200 | 115 | 52 | 142–146 (14) | $0.9072^{26}$ | $1.4263^{26}$ |
| Diethylene glycol | — | — | — | 250 (14) | — | — |
| Diethylene glycol ethyl ether | — | — | — | 140–145 (14) | — | — |
| Glycerol | — | — | (65–75) | 189–191[b] | $1.1193^{24}$ | $1.4395^{24}$ |
| *tert*-Ethylidenebisglycerol | 542 | 322 | 41.7 | 160–162 (14) | $1.1067^{24}$ | $1.4482^{20}$ |
| Glycerol methyl ether | 141 | 105 | 60 | 145–147 | $1.0098^{24}$ | $1.4145^{24}$ |
| Glycerol ethyl ether | — | — | — | 170–171 | — | — |
| Glycerol phenyl ether | 150 | 119 | 68 | 142–144 (14)<br>(m.p. 29°) | — | — |
| Bisethylidenepentaerythritol | 69 | 86 | 90 | 113 (14)<br>(m.p. 40°) | — | — |
| *tert*-Ethylidenemannite | 100 | 67 | 47 | 165–168 (17)<br>sublimed at 90° | — | — |
| Ethylene chlorohydrin | 304 | 250 | 71 | 106–107 (14) | — | — |
| Trimethylene chlorohydrin | 157 | 70 | 38 | 127–129 (14) | — | — |
| Glycerol chlorohydrin | 611 | 543 | 72 | 147–149 | $1.1720^{24}$ | $1.4410^{24}$ |
| Glycerol monoacetin | 260 | 153 | 49 | 91.5–92 (14)<br>200–201 (760) | $1.1110^{26}$ | $1.4323^{26}$ |
| Lactic acid | 240 | 179 | 61 | 149–151 | $1.074^{26}$ | $1.4120^{26}$ |
| 1-Hydroxyisobutyric acid | 148 | 125 | 71 | 150 ± 0.3 (745) | $1.0226^{26}$ | $1.4034^{28}$ |
| Bisethylidene tartrate | — | — | — | 122–128 (17) | | |
| Dimethyl tartrate | 184 | 172 | 81 | 137 ± 0.2 (16) | $1.2306^{27}$ | $1.4426^{27}$ |
| Diethyl tartrate | 162 | 137 | 74 | 147 ± 0.5 (18) | $1.1408^{25}$ | $1.1438^{25}$ |
| Methyl malate | 120 | 40 | 26 | 121–122 (15) | $1.1975^{26}$ | $1.4397^{26}$ |
| Ethyl malate | 118 | 50 | 30 | 125–130 (17) | $1.1215^{26}$ | $1.4402^{26}$ |
| Dimethyl citrate | 93 | 30 | 31 | (m.p. 73°C) | — | — |
| Mandelic acid | 82 | 62 | 64 | 142–144 (14) | $1.1681^{25}$ | $1.4145^{26}$ |
| Benzilic acid | 86 | 64 | 68 | 198–200 (17)<br>(m.p. 77°C) | — | — |

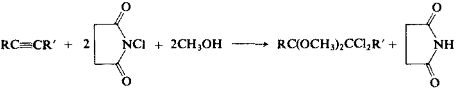
[a] The reaction is carried out using 5.0 gm of a 55–65% soln. of $BF_3$ in methanol and 1.0 HgO dissolved in it by heating. The flask is cooled, the alcohol added, mixed well and dry acetylene added while stirring. The theoretical amount of acetylene is used. [b] Mainly 1,2-isomer isolated by fractional distillation. The crude product contains 78% 1,2- and 22% 1,3-isomers. [Reprinted from J. A. Nieuwland, R. R. Vogt, and W. L. Foohey, *J. Amer. Chem. Soc.* **52**, 1018 (1930). Copyright 1930 by The American Chemical Society. Reprinted by permission of the copyright owner.]

with aqueous potassium carbonate, the product is extracted into ether, dried, and distilled to afford 104 gm (37%), b.p. 64°–65°C $n_D^{26}$ 1.3762.

Allylacetylene reacts with methanol to afford only 5,5-dimethoxy-1-alkenes [49]. Halogenated acetylenes do not interfere in this reaction [51]. For example, 1-bromoheptyne reacts with methanol under the same conditions to afford 1-bromo-2,2-dimethoxyheptane [51]. The chloro derivative reacts in a similar manner [51].

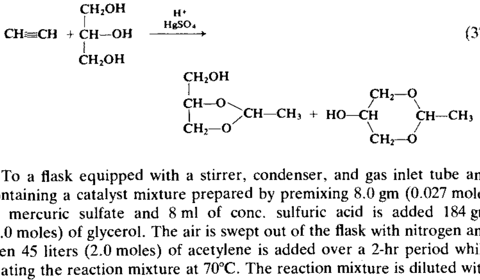
Cyclic acetals can be prepared by reacting acetylene with glycols in the presence of mercuric sulfate–sulfuric acid catalyst [52]. Some typical examples are shown in Table IX and Preparation 2-9.

Recently the reaction of acetylenes with *N*-chlorosuccinimide in methanol has been found to give the dichlorodimethyl ketals (Eq. 26) [53]. The latter are readily hydrolyzed in dilute acid to give the α,α′-dichloro ketones [53]. In equation (36) mercuric oxide was not reported to be required as a catalyst.



(36)

### 2-11. *Preparation of 2-Methyl-1,2- and -1,3-dioxolane-4-methanol (Ethylidene-glycerol)* [54]

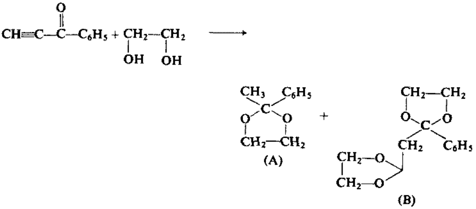


(37)

To a flask equipped with a stirrer, condenser, and gas inlet tube and containing a catalyst mixture prepared by premixing 8.0 gm (0.027 mole) of mercuric sulfate and 8 ml of conc. sulfuric acid is added 184 gm (2.0 moles) of glycerol. The air is swept out of the flask with nitrogen and then 45 liters (2.0 moles) of acetylene is added over a 2-hr period while heating the reaction mixture at 70°C. The reaction mixture is diluted with an equal volume of ether, filtered, neutralized with potassium carbonate, concentrated, and the residue distilled under reduced pressure to afford

234 gm (99%), b.p. 86–101°C 120 mm Hg), $n_D^{17}$ 1.4413-1.4532. The product contains a mixture of 1,3- and 1,2-dioxolane structures.

Recently Frame and Faulconer reported that propiolophenone reacts with ethylene glycol catalyzed by only *p*-toluenesulfonic acid (PTSA) to afford a mixture of two cyclic acetals [55].

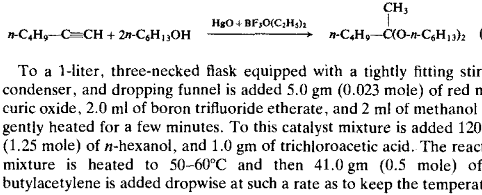


(38)

More PTSA favors formation of (A) and using very small amounts of PTSA gives mainly (B) [54]. Product (A) is probably obtained from (B) by a fragmentation reaction.

Some other examples of the preparation of acetals by the reaction of substituted acetylenes with alcohols are shown in Table X and are illustrated in Preparation 2-10.

### 2-12. *Preparation of 2,2-Dihexoxyhexane* [47d]



$$n\text{-}C_4H_9{-}C{\equiv}CH + 2n\text{-}C_6H_{13}OH \xrightarrow{HgO + BF_3O(C_2H_5)_2} n\text{-}C_4H_9{-}\overset{\displaystyle CH_3}{\overset{|}{C}}(O\text{-}n\text{-}C_6H_{13})_2 \quad (39)$$

To a 1-liter, three-necked flask equipped with a tightly fitting stirrer, condenser, and dropping funnel is added 5.0 gm (0.023 mole) of red mercuric oxide, 2.0 ml of boron trifluoride etherate, and 2 ml of methanol and gently heated for a few minutes. To this catalyst mixture is added 120 gm (1.25 mole) of *n*-hexanol, and 1.0 gm of trichloroacetic acid. The reaction mixture is heated to 50–60°C and then 41.0 gm (0.5 mole) of *n*-butylacetylene is added dropwise at such a rate as to keep the temperature at below about 70°C. After the addition the reaction mixture is stirred without heating until it reaches room temperature and then it is neutralized with methanolic sodium methoxide. The reaction mixture is fractionated to afford 92 gm (62%), b.p. 143–144°C (8.0 mm Hg), $n_D^{25}$ 1.4322.

## TABLE X

### Preparation of Acetals by the Reaction of Acetylene or Substituted Acetylenes with Alcohols

| Acetylene (moles) | ROH (mole) | Catalyst | Catalyst weight (gm) | Reaction conditions | | Acetal (%) | B.p., °C (mm Hg) m.p., °C | $n_D$ (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Temp. (°C) | Time (hr) | | | | |
| $CH{\equiv}CH$ | Glycerol | | | | | | | | |
| (2.0) | (2.0) | $HgSO_4$ | 8 | 70 | 2 | 99 | 86–101 | 1.4413– | *a* |
| | | $H_2SO_4$ conc. | 15 | | | | (20) | 1.4532 | |
| | | | | | | | | (17) | |
| $n\text{-}C_4H_9{-}C{\equiv}CH$ | *n*-Hexanol | | | | | | | | |
| (0.5) | (1.25) | HgO (red) | 5 | 50–70 | 1–2 | 62 | 143–144 | 1.4322 | *b* |
| | | $BF_3{\cdot}O(C_2H_5)_2$ | 2 | | | | (8) | (25) | |
| | | $CH_3OH$ | 2 | | | | | | |
| | | $CCl_3COOH$ | 1 | | | | | | |
| $C_2H_5{-}C{\equiv}CH$ | $CH_3OH$ | | | | | | | | |
| (1.0) | (2.0) | HgO (red) | 5 | 40 | 2 | 40 gm | 48–50 | 1.3899 | *c* |
| | | $BF_3{\cdot}O(C_2H_5)_2$ | 2 | | | | (100) | (28) | |
| | | $CH_3OH$ | 2 | | | | | | |
| $n\text{-}C_4H_9C{\equiv}CH$ | $CH_3OH$ | | | | | | | | |
| (0.5) | (1.25) | HgO (red) | 5 | 30–40 | 1–2 | 70 | 58–60 | 1.4053 | *d* |
| | | $BF_3{\cdot}O(C_2H_5)_2$ | 2 | | | | (30) | (25) | |
| | | $CH_3OH$ | 2 | | | | | | |
| $C_5H_{11}C{\equiv}C{-}Br$ | $CH_3OH$ | | | | | | | | |
| (0.194) | (5.0) | HgO | 2.5 | 0–15 | 24 | 60 | 88 (5) | 1.4531 | *e* |
| | | $BF_3{\cdot}O(C_2H_5)_2$ | 4 | | | | | (26) | |
| | | $CH_3OH$ | 10 | | | | | | |

*(continues)*

TABLE X (*Continued*)

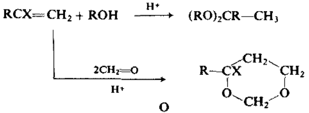
| Acetylene (moles) | ROH (mole) | Catalyst | Catalyst weight (gm) | Reaction conditions | | Acetal (%) | B.p., °C (mm Hg) m.p., °C | $n_D$ (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Temp. (°C) | Time (hr) | | | | |
| $C_5H_{11}C{\equiv}C{-}Cl$ | $CH_3OH$ | | | | | | | | |
| (0.194) | (5.0) | HgO | 2.5 | 0–15 | 24 | 30 | 80–82 | 1.4325 | *e* |
| | | $BF_3 \cdot O(C_2H_5)_2$ | 4 | | | | (8) | (25) | |
| | | $CH_3OH$ | 10 | | | | | | |
| $C_6H_5C{\equiv}C{-}CH_2CH{=}CH_2$ | $CH_3OH$ | | | | | | | | |
| (0.54) | (1.62) | HgO | 2 | 25 | 1–2 | 80 | 117–118 | 1.5011 | *f* |
| | | $BF_3 \cdot O(C_2H_5)_2$ | 1 | | | | (16) | (23) | |
| | | $CH_3OH$ | 2 | | | | | | |
| | | $CCl_3COOH$ | 1 | | | | | | |
| $CH_2{=}CH{-}C{\equiv}CH$ | $C_2H_5OH$ | | | | | | | | |
| (2.8) | (5.8) | HgO | 4 | 40 | 1–2 | 55 | 107–111 | 1.4142 | *g* |
| | | $BF_3 \cdot O(C_2H_5)_2$ | 5 | | | | (54) | (20) | |
| | | $CCl_3COOH$ | 2 | | | | 70–71 | | |
| | | $CH_3OH$ | 20 | | | | (5) | | |
| $CH_2{=}CH{-}C{\equiv}CH$ | $CH_3OH$ | | | | | | | | |
| (6.0) | (15) | HgO | 15 | 15–50 | 3 | 65 | 63–65 | 1.4082 | *h* |
| | | $BF_3 \cdot O(C_2H_5)_2$ | 4.5 | | | | | | |
| | | $CCl_3COOH$ | 2 | | | | | | |
| | | $CH_3OH$ | 10 | | | | | | |

---

[a] H. S. Hill, A. C. Hill, and H. Hibbert, *J. Amer. Chem. Soc.* **50**, 2242 (1928). [b] D. B. Killian, G. F. Hennion, and J. A. Nieuwland, *J. Amer. Chem. Soc.* **58**, 80 (1936). [c] D. B. Killian, G. F. Hennion, and J. A. Nieuwland, *J. Amer. Chem. Soc.* **56**, 1384 (1934). [d] G. F. Hennion, D. B. Killian, T. H. Vaughn, and J. A. Nieuwland, *J. Amer. Chem. Soc.* **56**, 1130 (1934). [e] P. A. McCusker and R. R. Vogt, *J. Amer. Chem. Soc.* **59**, 1307 (1937). [f] D. B. Killian, G. F. Hennion, and J. A. Nieuwland, *J. Amer. Chem. Soc.* **58**, 892 (1936). [g] R. O. Norris, J. J. Verbane, and G. F. Hennion, *J. Amer. Chem. Soc.* **61**, 887 (1939). [h] D. B. Killian, G. F. Hennion, and J. A. Nieuwland, *J. Amer. Chem. Soc.* **56**, 1786 (1934).

## D. Reactions of Alcohols or Aldehydes with Substituted Olefins

Olefins react with alcohols [56a–d] or formaldehyde [57a–c] to give acetals (Prins reaction; Eq. 40)



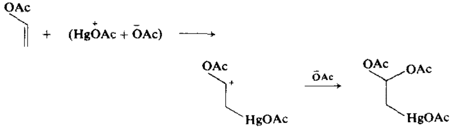
(40)

$X = H$ and $R = OR$ or $\overset{O}{\overset{\|}{O C}}CH_3$

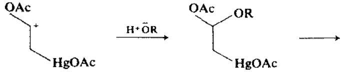
$X = O\underset{\underset{O}{\|}}{C}CH_3$ and $R = CH_3$

$X = R = CN$

Mercuric acetate catalyzes the reaction of vinyl esters with alcohols. The reaction may proceed through vinyl ether intermediates which react with alcohol to give acetals (Eqs. 41 and 42) [25b, 38].



(41)



(42)

$$ROCH{=}CH_2 + Hg(OAc)_2 \xrightarrow{H^+ \; ROH} (RO)_2CH{-}CH_3$$

Mercuric acetate and BF$_3$ are also effective catalysts. Some examples of this reaction are described in Tables XI and XII.

As shown in Table XII, the omission of the mercury catalyst leads to substantially lower yields. Mercuric oxide is preferred over mercuric sulfate, and mercuric phosphate is ineffective. Boron trifluoride etherate alone is ineffective. It serves to enhance the activity of the mercuric oxide catalyst. Preparative examples to illustrate this method are given in Preparations 2-11 and 2-12.

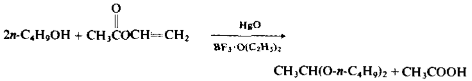
TABLE XI

PREPARATION OF ACETALS AND KETALS BY THE REACTION OF VINYL ESTERS WITH ALCOHOLS

| Acetate (moles) | Alcohol (moles) | Temp[a] (°C) | Acetal or ketal product | Observed yield (%) | Literature yield (%) |
|---|---|---|---|---|---|
| Vinyl (2.0) | Butyl (4.2) | 26–54 | Dibutyl acetal | 88 | 88 |
| Isopropenyl (14.0) | Methyl (29.4) | 29–54 | Dimethyl ketal | 53[b] | — |
| Isopropenyl (12.5) | Ethyl (37.4) | 30–50 | Diethyl ketal | 70[c] | 55 |
| Isopropenyl (10.0) | Butyl (22.0) | 10–55 | Dibutyl ketal | 83[d] | 63 |
| Isopropenyl (6.0) | Allyl (12.6) | 20–25 | Diallyl ketal | 50[e] | 32 |

[a] These values represent the temperature ranges from the start of ester addition until the temperatures were moderated by cooling. The temperatures were then controlled at 50° ± 5°C by cooling. For the preparation of diallyl ketal no cooling was required. [b] For this experiment, 3.6 gm $BF_3$ and 10.0 gm $Hg(OAc)_2$ were used. The ester addition time was 13 mins and the total reaction time was 23 mins. The yield is the average of three expts. for which the values varied from 51 to 55%. [c] For this experiment, 7.2 gm $BF_3$ and 18.4 gm $Hg(OAc)_2$ were used. The ester addition time was 16 min and the total reaction time was 18 min. The yield is the average of eight experiments for which the values varied from 68 to 73%. [d] For this experiment, 4.0 gm $BF_3$ and 12.0 gm $Hg(OAc)_2$ were used. The ester addition time was 10 min and the total reaction time was 20 min. The yield is the average of two experiments for which the values were 80 and 86%. [e] For this experiment, 4.0 gm $BF_3$ and 12.0 gm $Hg(OAc)_2$ were used. The ester addition time was 45 min and the total reaction time was 170 min. [Reprinted from D. H. Hirsh, R. I. Hoaglin, and D. G. Kubler, *J. Org. Chem.* **23**, 1083 (1958). Copyright 1958 by the American Chemical Society. Reprinted by permission of the copyright owner.]

## *2-13. Preparation of* n-*Butylacetal* [59]



$$2n\text{-}C_4H_9OH + CH_3\overset{\overset{\displaystyle O}{\|}}{C}OCH{=}CH_2 \xrightarrow[BF_3\cdot O(C_2H_5)_2]{HgO} CH_3CH(O\text{-}n\text{-}C_4H_9)_2 + CH_3COOH \qquad (43)$$

To a flask equipped with a stirrer, condenser, and dropping funnel and containing 148 gm (2.0 moles) of *n*-butanol is added 1.0 gm of red mercuric oxide and 1.0 ml of boron trifluoride etherate. Then 86.0 gm (1.0 mole) of vinyl acetate is added dropwise over a period of 10 min while maintaining the reaction temperature at 55°C with an ice bath. The reaction mixture is stirred for 1 hr, poured into a suspension of 56.0 gm (0.5 mole) of sodium carbonate in 250 ml of water, the upper layer separated, dried over anhydrous potassium carbonate, and distilled to afford 153 gm (89%), b.p. 74.5°–76°C (14 mm Hg), $n_D^{20}$ 1.4080.

TABLE XII

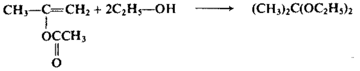
PREPARATION OF ACETALS AND KETALS BY THE REACTION OF ALCOHOLS WITH VINYL ACETATE OR ISOPROPENYL ACETATE[a]

| Vinyl ester (moles) | Alcohol (moles) | | Yield (%) | B.p., °C (mm Hg) | $n_D^{20}$ |
|---|---|---|---|---|---|
| Vinyl acetate | | *Catalyst:* 1.0 gm HgO and 1.0 ml $BF_3$ etherate<br>*Reaction conditions:* 50°–55°C, 2 hr | | | |
| 1.0 | $CH_3OH$ (2.0) | | 84 | 62.5–64.0 (760) | 1.3665 |
| 1.0 | $C_2H_5OH$ (2.0) | | 88 | 103–104 (760) | 1.3809 |
| 1.0 | $i$-$C_3H_2OH$ (2.0) | | 38 | 126.5 (760) | 1.3890 |
| 1.0 | $n$-$C_4H_9OH$ (2.0) | | 89 | 74.5–76.0 (14) | 1.4080 |
| 1.0 | $n$-$C_4H_9OH$ (2.0)[b] | | 29 | 74.5–76.0 (14) | 1.4080 |
| 1.0 | $CH_2{=}CH{-}CH_2OH$ (2.0) | | 85 | 148.0–149.5 (760) | 1.4218 |
| Isopropenyl acetate | | | | | |
| 1.0 | $C_2H_5OH$ (2.0) | | 55 | 113.0–113.5 (760) | 1.3891 |
| 1.0 | $n$-$C_4H_9OH$ (2.0) | | 63 | 64.0–64.5 (3) | 1.4120 |
| 1.0 | $CH_2{=}CH{-}CH_2OH$ (2.0)[b] | | 32 | 61–62 (26) | 1.4262 |

---

[a] Data taken from W. J. Croxall, F. J. Glavis, and H. T. Neher, *J. Amer. Chem. Soc.* **70**, 2805 (1948). [b] No catalyst.

## 2-14. *Preparation of the Diethyl Ketal of Acetone (2,2-Diethoxypropane)* [56a]

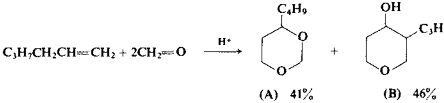


$$CH_3{-}\underset{\substack{|\\ OCCH_3\\ \| \\ O}}{C}{=}CH_2 + 2C_2H_5{-}OH \longrightarrow (CH_3)_2C(OC_2H_5)_2 \qquad (44)$$

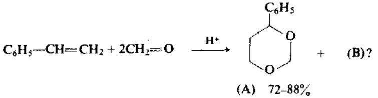
To a flask equipped as in Preparation 2-11 and containing 1725 gm (37.5 moles) of ethanol, 18.4 gm (0.058 mole) of mercuric acetate, and 28 ml of 26% boron fluoride etherate (26%) at 30°C is added dropwise over a 15 min period at 45–50°C, 1250 gm (12.5 moles) of isopropenyl acetate. After the reaction 2200 gm of 25% sodium hydroxide is added, the organic layer separated, washed first with 400 ml of 0.01 *N* sodium hydroxide, dried, and distilled to afford 1140 gm (69%), b.p. 110–113 C (760 mm Hg).

More recently it has been reported that vinyl acetate can be reacted with chlorine and methanol to produce chloroacetaldehyde dimethacrylacetal, in a semicontinuous process [56e].

The acid-catalyzed reaction of formaldehyde with olefins is known as the Prins reaction [60]. The major products are (A) 1,3-dioxanes (or *m*-dioxanes) and (B) tetrahydropyranols (Eqs. 45 and 46).



(45)



(46)

Some typical examples of this reaction are summarized in Table XIII and the method is outlined in Preparation 2-13.

## *2-15. General Procedure for the Condensation of 1-Olefins with Formalin* [60] (see Eqs. 35 and 36).

To an autoclave constructed of Hastelloy C7 and equipped with a stirrer is added 2.0 moles of olefins, 400 gm (4.9 moles) of 37% formalin and 5 ml of sulfuric acid. The autoclave is sealed, flushed with nitrogen, heated at 150°C for 6 hr and cooled. The reaction mixture is extracted three times with ether, dried, and distilled. A vapor-phase chromatogram of the crude ether solution gives the relative proportions of the products.

Some typical examples illustrating the utility of Procedure 2-13 are shown in Table XIII.

Chlorovinyl ketones react with alkaline alcoholic solutions to afford acetals. For example, β-chlorovinyl isoamyl ketone reacts with methanolic sodium hydroxide to afford β-ketoisooctaldehyde dimethyl acetal in 80–

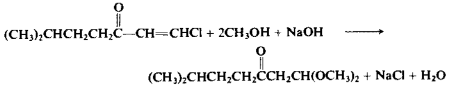
TABLE XIII

REACTION OF OLEFINS WITH FORMALDEHYDE TO GIVE ACETALS

| R—CH═CH$_2$ R = (moles) | CH$_2$═O 37% (moles) | Conc. H$_2$SO$_4$ catalyst (gm) | Reaction conditions Temp. (°C) | Time (hr) | Yield[a] (%) | B.p., °C (mm Hg) | $n_D$ 20°C | Ref. |
|---|---|---|---|---|---|---|---|---|
| | | | Atmospheric pressure | | | | | |
| C$_6$H$_5$ (3.0) | 8.3 | 88.3 | 100 | 6 | 72–88 (A) | 96–103 (2) | 1.5300<br>1.5311 | b |
| | | | Autoclave reactor | | | | | |
| C$_3$H$_7$ (2.0) | 4.9 | 9.2 | 150 | 6 | 46 (A) | 60–61 (16) | 1.4278 | c |
| | | | | | 42 (B) | 112–114 (16) | 1.4595 | |
| C$_4$H$_9$ | 4.9 | 9.2 | 150 | 6 | 41 (A) | 62–63 (8) | 1.4355 | c |
| | | | | | 46 (B) | 105–106 (8) | 1.4591 | |
| C$_6$H$_{13}$ (2.0) | 4.9 | 9.2 | 150 | 6 | 43 (A) | 105–107 (2) | 1.4397 | c |
| | | | | | 45 (B) | 95–99 (0.5) | 1.4585 | |
| C$_8$H$_{17}$ (2.0) | 4.9 | 9.2 | 150 | 6 | 40 (A) | 132–134 (12) | 1.4462 | c |
| | | | | | 47 (B) | 168–170 (12) | 1.4588 | |
| C$_{10}$H$_{21}$ (2.0) | 4.9 | 9.2 | 150 | 6 | 42 (A) | 128–130 (1.5) | — | c |
| | | | | | 46 (B) | 150–154 (1.5) | 1.4590 | c |

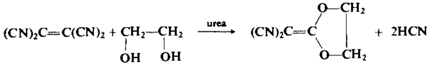
[a] For (A) and (B) type see Eqs. (35) and (36). [b] R. L. Shriner and P. R. Ruby, *Org. Syn. Coll.* **4**, 786 (1963). [c] P. R. Stapp, *J. Org. Chem.* **35**, 2419 (1970).

90% yield (Eq. 47) [61a,b]. Other examples are described in the literature [62a,b].



$$(CH_3)_2CHCH_2CH_2\overset{O}{\overset{\|}{C}}—CH═CHCl + 2CH_3OH + NaOH \longrightarrow (CH_3)_2CHCH_2CH_2\overset{O}{\overset{\|}{C}}CH_2CH(OCH_3)_2 + NaCl + H_2O \quad (47)$$

Recently tetracyanoethylene has been shown to react with glycols to afford dicyanoketene alkylene acetals. For example, tetracyanoethylene reacts with ethylene glycol in the presence of urea to afford a 77–85% yield of dicyanoketene ethylene acetal (Eq. 48) (63, 64).

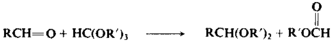


(48)

In a related manner methanol reacts to give dicyanoketene dimethyl acetal and ethanol gives dicyanoketene diethyl acetal [64].

### E. Reaction of Ortho Esters with Aldehydes

The acid-catalyzed reaction of aldehydes with orthoformates affords the acetal of the aldehyde and alkyl formate as described in Eq. (49) and Table XIV.

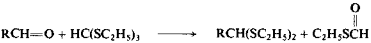


$$\mathrm{RCH{=}O + HC(OR')_3 \longrightarrow RCH(OR')_2 + R'O\overset{\overset{O}{\|}}{C}H} \qquad (49)$$

The acid catalysts that are effective are ammonium chloride [65, 66], anhydrous hydrogen chloride [66, 67], and conc. sulfuric acid [66].

The reaction mixture is neutralized before work-up because the acetals readily undergo hydrolysis.

In place of alkyl orthoformate, the methyl and ethyl esters of orthosilicic acid [68] may be used, but care must be taken to remove compounds of silicon. The use of ethyl thioorthoformate results in the production of dithioacetals (see Table XV)



$$\mathrm{RCH{=}O + HC(SC_2H_5)_3 \longrightarrow RCH(SC_2H_5)_2 + C_2H_5S\overset{\overset{O}{\|}}{C}H} \qquad (50)$$

The reaction fails with sulfuric acid catalysis when paraformaldehyde, paraldehyde, or crotonaldehyde is used with ethyl orthoformate [69]. Crotonaldehyde reacts with ethyl orthoformate under ammonium nitrate catalysis to afford crotonaldehyde diethyl acetal in 68% yield [70]. In addition the reaction gives only a trace or poor yields of acetal product with ortho esters other than ethyl orthoformate, as seen in Table XV. The reaction usually proceeds well with aliphatic (including acrolein) and aromatic aldehydes [71] except where steric or electronic effects interfere. *p*-Methoxy- and *m*-aminobenzaldehyde afford the diethyl acetals in good yields [72a,b].

Acrolein reacts with ethyl orthoformate under ammonium nitrate catalysis to give acrolein diethyl acetal in 72–80% yield [70, 73]. Acrolein diethyl acetal reacts with ethyl orthosilicate in the presence of anhydrous hydrogen chloride to afford the saturated acetal, $\beta$-ethoxypropionaldehyde diethyl acetal, in 76% [74]. Several examples of the reaction of aldehydes with triethyl orthoformate shown in Table XVI and the preparative details are illustrated in Preparations 2-16 and 2-17.

## TABLE XIV

### PREPARATION OF ACETALS FROM THE REACTION OF ALDEHYDES WITH ORTHO ESTERS[a,b]

| Aldehyde | Ortho Ester | Product | Yield (%) | Comment | B.p., °C (mm Hg) | $n_D$ (°C) |
|---|---|---|---|---|---|---|
| $CH_3CHO$ | $HC(OC_2H_5)_3$ | $CH_3CH(OC_2H_5)_2$ | 58 | — | 102 (760) | 1.3797 (23) |
| $CH_3CHO$ | $HC(OC_3H_7)_3$ | $CH_3CH(OC_3H_7)_2$ | 43 | — | 62–63 (42) | 1.3939 (26) |
| $CH_3CHO$ | $HC(OC_4H_9)_3$ | $CH_3CH(OC_4H_9)_2$ | 34 | — | 95–96 (30) | 1.4045 (25) |
| $C_6H_5CHO$ | $HC(OC_2H_5)_3$ | $C_6H_5CH(OC_2H_5)_2$ | 66 | — | 222 (760) | 1.4721 (24.5) |
| $(HCHO)_x$ | $HC(OC_2H_5)_3$ | None | 0 | Paraform used | — | — |
| $(C_2H_4O)_3$ | $HC(OC_2H_5)_3$ | None | 0 | Paraldehyde used | — | — |
| $(C_2H_4O)_3$ | $HC(OC_2H_5)_3$ | None | 0 | Paraldehyde, much polymerization | — | — |
| $CH_3CH{=}CHCHO$ | $HC(OC_2H_5)_3$ | None | 0 | Much polymerization | | |
| $C_6H_5CHO$ | $HC(OC_3H_7)_3$ | $C_6H_5CH(OC_3H_7)_2$ | 40 | — | 242 (760) | 1.4761 (25.5) |
| $C_2H_5CHO$ | $HC(OC_2H_5)_3$ | $C_2H_5CH(OC_2H_5)_2$ | 40 | — | 123 (740) | 1.3872 (25.5) |
| $C_2H_5CHO$ | $HC(OC_4H_9)_3$ | None | 0 | — | — | — |
| $C_2H_5CHO$ | $HC(OC_3H_7)_3$ | $C_2H_5CH(OC_3H_7)_2$ | 13 | — | 157–160 (760) | 1.4038 (24) |
| $C_6H_5CH{=}CHCHO$ | $HC(OC_2H_5)_3$ | None | 0 | Polymerization | — | — |
| $CH_3CHO$ | $CH_3C(OC_2H_5)_3$ | $CH_3CH(OC_2H_5)_2$ | trace | — | — | — |
| $CH_3CHO$ | $CH_3C(OC_2H_5)_3$ | $CH_3CH(OC_2H_5)_2$ | trace | — | — | — |
| $C_6H_4(CH_3)CHO$-*o* | $HC(OC_2H_5)_3$ | $C_6H_4(CH_3)CH(C_2H_5)_2$-*o* | trace | — | 125 (37) | 1.4949 (23) |
| $C_6H_4(CH_3)CHO$-*m* | $HC(OC_2H_5)_3$ | $C_6H_4(CH_3)CH(OC_2H_5)_2$-*m* | 58 | — | 190 (750.5) | 1.4841 (25) |
| $C_6H_4(CH_3)CHO$-*p* | $HC(OC_2H_5)_3$ | $C_6H_4(CH_3)CH(OC_2H_5)_2$-*p* | 16 | — | 105–106 (22) | 1.4845 (22) |

[a] See Table XV footnote for source.

[b] Catalyst, one drop conc. $H_2SO_4$.

## TABLE XV

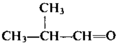
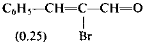
### PREPARATION OF THIOACETALS

| Reactants | Product | Yield (%) | B.p., °C (mm Hg) | $n_D$ (°C) |
|---|---|---|---|---|
| 0.15 mole $HC(SC_2H_5)_3$ + 0.31 mole $CH_3CHO$ | $CH_3CH(SC_2H_5)_2$ | 33⅓ | 186–189 (753) | 1.4985 (28) |
| 0.30 mole $HC(SC_2H_5)_3$ + 0.60 mole $CH_3CHO$ | $CH_3CH(SC_2H_5)_2$ | 9[a] | 186–189 (753) | 1.4985 (28) |
| 2.0 mole $C_2H_5SH$ + 1.0 mole $CH_3CHO$ | $CH_3CH(SC_2H_5)_2$ | 6[a] | 186–189 (753) | 1.4985 (28) |
| 0.06 mole $HC(SC_3H_7)_3$ + 0.12 mole $CH_3CHO$ | $CH_3CH(SC_3H_7)_2$ | 10 | 116 (13) | 1.4950 (23.5) |

[a] Very small fraction taken for analysis. [Table XIV and XV are reprinted in part from H. W. Post, *J. Org. Chem.* **5**, 244 (1940). Copyright 1940 by the American Chemical Society. Reprinted by permission of the copyright owner.]

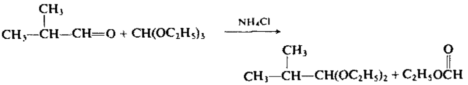
## TABLE XVI

### REACTION OF ALDEHYDES WITH TRIETHYL ORTHOFORMATE TO GIVE ACETALS

| RCH=O (moles) | $HC(OC_2H_5)_3$ (moles) | Solvent, $C_2H_5OH$ (ml) | Catalyst (gm) | Reaction conditions Temp. (°C) | Reaction conditions Time (hr) | Yield (%) | B.p., °C (mm Hg) | $n_D$ (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
|  $CH_3-CH(CH_3)-CH=O$ (1.0) | 1.0 | 400 | $NH_4Cl$ (4) | 78 | $\frac{3}{4}$ | 61 | 134–138 (760) | — | a |
| $CH_2=CH-CH=O$ (0.79) | 0.97 | 50 | $NH_4NO_3$ (3) | 25 | 6–8 | 72–80 | 120–125 (760) | 1.3980–1.4070 (25) | b |
| $CH_3CH=CH-CH=O$ (0.79) | 0.97 | 50 | $NH_4NO_3$ (3) | 25 | 6–8 | 68 | 145–147 (706) | 1.4090 (25) | b |
|  $C_6H_5-CH=C(Br)-CH=O$ (0.25) | 0.30 | 40 | $NH_4Cl$ (0.5) | 78 | 1–2 | 82–86 | 146–149 (5) | 1.5500 (22) | c |

[a] F. M. Hamer and R. J. Rathbone, *J. Chem. Soc.* 597 (1945). [b] J. A. Van Allan, *Org. Syn. Coll.* **4**, 21 (1963). [c] C. F. H. Allen and C. O. Edens, Jr., *Org. Syn. Coll.* **3**, 731 (1955).

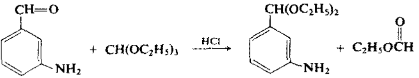
### *2-16. Preparation of Isobutyraldehyde Diethyl Acetal* [75]



$$CH_3-\overset{CH_3}{\overset{|}{C}}H-CH{=}O + CH(OC_2H_5)_3 \xrightarrow{NH_4Cl} CH_3-\overset{CH_3}{\overset{|}{C}}H-CH(OC_2H_5)_2 + C_2H_5O\overset{O}{\overset{\|}{C}}H \quad (51)$$

To a flask equipped with a 12-in. Vigreux column and distillation head is added 144 gm (1.0 mole) of isobutyraldehyde, 296 gm (1.0 mole) of ethyl orthoformate, 400 ml of ethanol, and 4.0 gm of ammonium chloride. The reaction mixture is heated under reflux on a steam bath for 15 min and then fractionally distilled to afford 179 gm (61%), b.p. 134°–138°C (760 mm Hg).

### *2-17. Preparation of* m-*Aminobenzaldehyde Diethyl Acetal* [76]



(52)

To a flask equipped with a magnetic stirrer and containing 25 gm (0.21 mole) of *m*-aminobenzaldehyde is added 175 gm of 5% alcoholic hydrogen chloride, and 75 gm (0.51 mole) of triethyl orthoformate. The reaction mixture is stirred at room temperature in the closed flask for 12 hr, and then 8.0 gm (0.12 mole) of sodium ethoxide in 175 ml of ethanol is added with stirring. The reaction mixture is diluted with 4–5 volumes of water, and the precipitated yellow oil extracted into ether. The ether solution is dried and concentrated at temperatures below 60°C to afford 36 gm (88%). Distillation of this crude product, b.p. 137°–139°C (5.0 mm Hg) indicates it is almost pure acetal. Distillation is usually not recommended since decomposition takes place and probably gives a polymer due to the elevated temperature reactivity of the amino group with the acetal functional group.

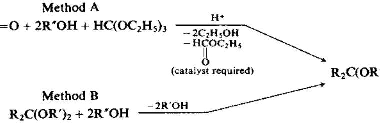
## F. Reaction of Ortho Esters with Ketones

Ketones also react with alkyl orthoformate to afford ketals. For example, *p*-bromoacetophenone reacts with ethyl orthoformate to produce the ketal in 65% yield [77]. The mechanism of this reaction has been studied [77b].

The reaction of ethyl $\alpha$-keto-*n*-butyrate and ethyl $\alpha$-keto-*n*-valerate react with ethyl orthoformate in ethanolic hydrochloric acid solution to give the diethyl ketals in good yield. The use of ethylene glycol–hydrogen chloride affords the ethylene ketal in good yield if the ethanol is removed by distillation [78].

Post [69] reported that in the preparation of ketals from orthoformates an increase in the size of the trialkyl part of the molecule decreases the yield. Dykstra [79] reported that good yields of ketals are obtained starting with tripropyl and tributyl orthoformates; however, the exact values were not given.

The ketal–alcohol and the orthoformate–alcohol interchanges do not always require a catalyst; however, an acidic catalyst is helpful. The following two interchange methods exist for the preparation of ketals: (A) direct reaction of the ketone with alcohol in the presence of triethyl orthoformate and *p*-toluenesulfonic acid and (B) reaction of dialkyl ketals with an alcohol in the presence or absence of acid.



Method A

$$R_2C{=}O + 2R''OH + HC(OC_2H_5)_3 \xrightarrow[-2C_2H_5OH,\ -H\overset{\displaystyle O}{\overset{\|}{C}}OC_2H_5\ (\text{catalyst required})]{H^+} R_2C(OR'')_2 \quad (53)$$

Method B

$$R_2C(OR')_2 + 2R''OH \xrightarrow{-2R'OH} R_2C(OR'')_2$$

In Method A, the components are heated together. The lower-boiling materials are steadily removed through a packed column to first give ethyl formate and then the ethanol. The reaction proceeds well and the data for seven ketones are shown in Table XVII, where Method A is compared to Method B.

Secondary alcohols do not react either in Methods A and B to give ketals derived from secondary alcohols [80]. These ketals cannot also be prepared by the addition of secondary alcohols to acetylenic compounds [47d]. Cyclic ketals (dioxolanes) can be prepared from secondary alcohols, such as from acetone and 2,3-butanediol [81]. In contrast, di-tertiary alkyl derivatives of acetals [82], and tri-*sec*-alkyl derivatives of orthoformates [48] have been reported. The latter cannot be used to give the di-*sec*-butyl ketals since the orthoester is recovered unchanged [80].

Typical preparative examples are described in Preparations 2-18 to 2-22.

## *2-18. General Procedure for the Preparation of Ketals by Method A*

*a. Single-step procedure.* A solution of 0.3 mole of triethyl orthoformate, 0.25 mole of ketone, approximately 1.5 moles of alcohol (higher-boiling than ethanol), and 300 mg of *p*-toluenesulfonic acid is slowly heated so that the removal of ethyl formate through a 30–50-cm glass helicesfilled column begins after 1 hr. Ethyl formate and ethanol are then

TABLE XVII

PREPARATION OF KETALS STARTING WITH TRIETHYL ORTHOFORMATE

| Ketone | Alcohol | Method A or B (see Eq. 43 and Preps. 2-16 and 2-17) | Yield (%) | B.p., °C (mm Hg) | $n_D$ (°C) | Ref. |
|---|---|---|---|---|---|---|
| Acetone | Ethanol | B | — | 112–113 (760) | 1.3865 (24) | *a* |
| Acetone | *n*-Butanol | A | 81[b] | 64 (2.3) | 1.4128 (20) | *c* |
| | | B | 79 | | | *c* |
| Acetone | *n*-Octanol | A | 73 | 116 (0.05) | 1.4360 (20) | *c* |
| Acetone | *n*-Pentanol | A | 79 | 74.5 (1.2) | 1.4207 (20) | *c* |
| | | B | 86 | | | |
| 3-Pentanone | *n*-Butanol | A | 84 | 72.4 (1.5) | 1.4212 (25) | *c* |
| Cyclohexanone | *n*-Butanol | A | 89 | 89.5 (1.9) | 1.4423 (25) | *c* |
| Propiophenone | Ethanol | B | — | 92–93 (8) | 1.4860 (24) | *a* |
| Acetophenone | Ethanol | B | — | 93–95 (12) | 1.4778 (24) | *a* |
| Acetophenone | *n*-Butanol | A | 52[d] | 85 (0.3) | 1.4723 (30) | *c* |
| *p*-Bromoacetophenone | Ethanol | B | 65 | 153–155 (24) | — | *e* |
| β-Ethoxyethyl methyl ketone | Ethanol | B | 92 | 72–75 (9) | — | *f* |

[a] T. H. Fife and L. Hagopian, *J. Org. Chem.* **31**, 1772 (1966). [b] Substitution of triethyl orthoacetate for triethyl orthoformate gave a 76% yield. [c] C. A. Mackenzie and J. H. Stocker, *J. Org. Chem.* **20**, 1695 (1955). [d] *syn*-Triphenylbenzene and dypnone isolated in small amounts. [e] C. E. Kaslow and W. R. Lawton, *J. Amer. Chem. Soc.* **72**, 1723 (1950). [f] H. B. Dykstra, *J. Amer. Chem. Soc.* **57**, 2255 (1935).

removed at a steady rate until the head temperature indicates removal is complete. A few milliliters of a dilute solution of sodium in the higher-boiling alcohol is added to the slightly cooled solution, which is then washed three times with 50 ml of water and dried over potassium carbonate. The dry solution is fractionally distilled.

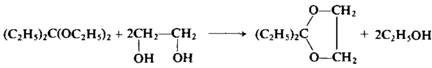
*b. Preformed orthoformate procedure.* A solution of 0.3 mole of triethyl orthoformate and approximately 1.5 moles of alcohol (higher-boiling than ethanol) is heated and the ethanol is removed through a 30–50 cm glass helices-filled column until the theoretical amount has been distilled (3 hr for replacement by 1-butanol, 7 hr for 2-butanol). The mixture is cooled to 50°C or less and 0.25 mole of ketone and 300 mg of *p*-toluenesulfonic acid are added. The mixture is heated slowly so that refluxing is obtained in 60–90 min. The mixture is cooled, neutralized, and the product isolated as in Procedure *a*.*

### *2-19. Preparation of the Dipentyl Ketal of Acetone by Method B* [80]

$$(CH_3)_2C(OC_4H_9)_2 + 2C_5H_{11}OH \longrightarrow (CH_3)_2C(OC_5H_{11})_2 + 2C_4H_9OH \qquad (54)$$

To a flask containing 47.6 g (0.25 mole) of the dibutyl ketal of acetone is added 100 ml (0.81 mole) of 1-pentanol and the mixture refluxed. The *n*-butanol is removed by distillation over a 4-hr period through a $1\frac{1}{2}$-ft glass helices-packed column at 117°–118°C. The residue is transferred to a flask with a $\frac{1}{2}$-ft fractionating column and distilled to give 41.1 gm (76%), b.p. 119°–122°C (760 mm Hg), $h_{\mathrm{D}}^{20}$ 1.4202.

### *2-20. Preparation of 2,2-Diethoxy-1,3-dioxolane by Method B* [80]



(55)

To a flask equipped with a mechanical stirrer, 1-ft distillation column, and distillation head is added 32 gm (0.20 mole) of the diethyl ketal of 3-pentanone and 37.2 gm (0.60 mole) of ethylene glycol. The mixture is heated and the ethanol (18.4 gm) is removed over a 1-hr period. The residue is distilled under reduced pressure to afford 24 gm (94%), b.p. 61.3°C (50 mm Hg), $n_{\mathrm{D}}^{20}$ 1.4190.

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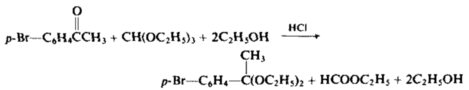
* Procedures *a* and *b* reprinted from C. A. MacKenzie and J. H. Stocker, *J. Org. Chem.* **20,** 1695 (1955). Copyright 1955 by the American Chemical Society. Reprinted by permission of the copyright owner.

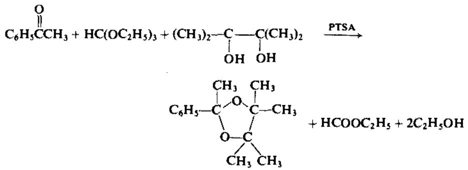
### 2-21. *Preparation of* p*-Bromoacetophenone Diethyl Acetal by Method A* [83]



$$p\text{-Br}{-}C_6H_4\overset{\overset{\displaystyle O}{\|}}{C}CH_3 + CH(OC_2H_5)_3 + 2C_2H_5OH \xrightarrow{HCl} p\text{-Br}{-}C_6H_4{-}\overset{\overset{\displaystyle CH_3}{|}}{C}(OC_2H_5)_2 + HCOOC_2H_5 + 2C_2H_5OH \quad (56)$$

To a flask containing 20 gm (0.1 mole) of *p*-bromoacetophenone is added 24.0 gm (0.16 mole) of triethyl orthoformate in 65 ml of absolute ethanol which contains 0.1 gm of HCl. The solution is allowed to stand at room temperature for 24 hr, neutralized with sodium ethoxide, concentrated, and the residue distilled under reduced pressure to afford 18.2 gm (65%), b.p. 153°–155°C (24 mm Hg).

### 2-22. *Preparation of 2-Phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane by Method A* [84a]



(57)

To a flask containing 120.1 gm (1.0 mole) of acetophenone is added 148.0 gm (1.0 mole) of triethyl orthoformate, 118.0 gm (1.0 mole) of tetramethylethylene glycol and 0.1 gm of *p*-toluenesulfonic acid. After 12 hr at room temperature the ethanol is removed by distillation and the residue is added to 200 ml of benzene. The benzene solution is washed with 0.1 *M* aqueous sodium hydroxide, washed with water, dried, concentrated, and the residue distilled under reduced pressure to afford the product b.p. 77°–78°C (1.2 mm), $n_D^{24}$ 1.48900. The percent yield is not given but the preparation is shown here for information only since it illustrates the use of Method A with glycols.

Recently, it has been reported that diaryl ketones can be made to undergo the formation of ketals by the reaction of alcohols and orthoformate if triflic acid is used as a catalyst [84b]. The yields range from 81–97%.

$$\mathrm{R^1R^2C{=}O} \xrightarrow[\substack{\mathrm{CH_3NO_2\ Solvent} \\ \mathrm{CF_3SO_3H\ Catalyst}}]{\mathrm{R^3OH,\ CH(OR^3)_3}} \mathrm{R^1R^2C(OR^3)_2} \tag{58}$$

For example: $R^1 = R^2$ 4—$ClC_6H_4$ or 3—$ClC_6H_4$ etc.

$R^3 = CH_3$ or $C_2H_5$

### *2-23. Preparation of Bis(3-nitrophenyl)dimethoxymethane* [84b]

$$\mathrm{(3{-}Cl{-}C_6H_4)_2C{=}O + CH_3OH} \xrightarrow[\substack{\mathrm{CH_3NO_2} \\ \mathrm{CF_3SO_3H} \\ \mathrm{-2CH_3OH} \\ -\mathrm{H}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{OCH_3}}]{\mathrm{CH(OCH_3)_3}} \mathrm{(3{-}ClC_6H_4)_2C(OCH_3)_2} \tag{59}$$

To a flask is added 2.0 g (7.4 mmole) 3,3'-dinitrobenzophenone, 7.80 g (74.0 mmole) trimethyl orthoformate, and 2.37 g (74.0 mmole) in 20 ml nitromethane. The mixture is cooled to 5°C in an ice-water bath and 220 mg (1.5 mmole) triflic acid is added dropwise. The ice bath is then replaced by an oil bath and the reaction mixture heated to reflux and held there for 4 hr. The mixture is cooled to room temperature and poured into a separatory funnel containing 50 ml saturated $NaHCO_3$ solution. The resulting mixture is ether extracted using 2 × 50 ml, the organic phase separated, and dried over $MgSO_4$. The solvent is then evaporated under reduced pressure to afford a white solid. Recrystallization from 95% ethanol gives 2.1 g (90%), m.p. 126°C.

Analysis: $C_{15}H_{14}N_2O_6$ (MW 318.3): H' NMR ($CHCl_3$/TMS) 3.17 (3, 6H); 7.52 (t, 2H, J = 8.0); 7.28 (*m*, 4H); 8.15 (*d*, 2H, J = 7.8) MS (70eV) $m/z$ $(M^+ - OR^3) = 287$.

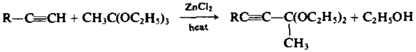
## G. Reaction of Ortho Esters with Acetylenic Compounds

Free acetylene and substituted acetylenes react with ortho esters in a one-step catalytic process (Eq. 48). Molar equivalents of the acetylene and ortho esters are heated in the presence of catalytic amounts of zinc chloride, zinc iodide, zinc nitrate, or cadmium iodide at atmospheric pressure while the alcohol is removed as it forms. The alcohol begins to distill from the flask when the pot temperature reaches about 200°C. The use of free acetylene or other low-boiling acetylenes such as 1-hexyne requires the reaction to be carried out under autogenous pressure in a rocker bomb. Acetylene itself reacts with triethyl orthoformate to give the diacetal, acetylenedicarboxaldehyde bis-(diethyl acetal) and several other byproducts (Eq. 61).

$$RC{\equiv}CH + HC(OC_2H_5)_3 \xrightarrow[heat]{ZnCl_2} RC{\equiv}C{-}CH(OC_2H_5)_2 + C_2H_5OH \qquad (60)$$

$$\begin{aligned} HC{\equiv}CH + HC(OC_2H_5)_3 \xrightarrow{ZnCl_2} & (C_2H_5O)_2CH{-}C{\equiv}C{-}CH(OC_2H_5)_2 + \qquad (61) \\ & HC{\equiv}C{-}CH(OC_2H_5)_2 + \\ & (C_2H_5O)_2CH{-}CH_2CH(OC_2H_5)_2 \end{aligned}$$

The use of triethyl orthoacetate or trimethyl orthovalerate led to the formation of acetylenic ketals.



$$R{-}C{\equiv}CH + CH_3C(OC_2H_5)_3 \xrightarrow[heat]{ZnCl_2} RC{\equiv}C{-}\underset{CH_3}{\underset{|}{C}}(OC_2H_5)_2 + C_2H_5OH \qquad (62)$$

Tetraethyl orthocarbonate reacted under the same conditions as for the ortho esters but gave acetylenic ortho ester products, as shown in Eq. (63).

$$RC{\equiv}CH + C(OC_2H_5)_4 \xrightarrow[heat]{ZnCl_2} RC{\equiv}C{-}C(OC_2H_5)_3 + C_2H_5OH \qquad (63)$$

Some typical examples illustrating the usefulness of this reaction are shown in Table XVIII. The method is described in detail in Preparation 2-24.

Acetylene also reacts with the higher ortho esters to give low yields of products that were not fully characterized [85]. Based on analogy, these products are ketal derivatives but further work is required to clarify this aspect of this reaction.

Acetylenic acetals can also be prepared by the reaction of an acetylenic Grignard reagent or a sodium acetylide with an orthoformate ester (Eqs. 64 and 65) [86a–d]. The reaction of phenylacetylenic Grignard reagent with tetraethyl orthocarbonate also gives the corresponding ortho ester (Eq. 66) [87].

$$RC{\equiv}C{-}MgX + HC(OC_2H_5)_3 \longrightarrow RC{\equiv}C{-}CH(OC_2H_5)_2 + MgXOC_2H_5 \qquad (64)$$

$$RC{\equiv}C{-}Na + HC(OC_2H_5)_3 \longrightarrow RC{\equiv}C{-}CH(OC_2H_5)_2 + NaOC_2H_5 \qquad (65)$$

$$RC{\equiv}C{-}MgX + C(OC_2H_5)_4 \longrightarrow RC{\equiv}C{-}C(OC_2H_5)_3 + MgXOC_2H_5 \qquad (66)$$

### *2-24. Preparation of Phenylpropiolaldehyde Diethyl Acetal* [85, 88]

$$C_6H_5C{\equiv}CH + CH(OC_2H_5)_3 \xrightarrow[heat]{ZnI_2} C_6H_5C{\equiv}C{-}CH(OC_2H_5)_2 + C_2H_5OH \qquad (67)$$

To a flask equipped with a 12-in. Vigreux column and distillation head is added 74.0 gm (0.50 mole) of triethyl orthoformate, 51.0 gm (0.50 mole)

## TABLE XVIII

### CATALYTIC SYNTHESIS OF ETHYNYL ACETALS, KETALS, AND ORTHO ESTERS FROM MONOSUBSTITUTED ACETYLENES

| Acetylene | Ortho ester | Reaction conditions | Product[a] | Yield (%) | Carbon, % Calcd. (Found) | Hydrogen, % Calcd. (Found) | B.p., °C (mm Hg) | $n_D^{25}$ |
|---|---|---|---|---|---|---|---|---|
| $n$-$C_4H_9C{\equiv}CH$ | $HC(OC_2H_6)_3$ | 190°C/3 hr in closed bomb; $ZnI_2/ZnCl_2$ catalyst; 0.7 mole scale | $n$-$C_4H_9C{\equiv}CCH(OC_2H_5)_2$ | 32.0 | 71.7<br>(71.8) | 10.9<br>(10.8) | 90 (10) | 1.4327 |
| $C_2H_5C{\equiv}CH$ | $CH_2C(OC_2H_5)_3$ | Ethyl alcohol removed in 3.7 hr; $ZnCl_2$ catalyst; 0.4 mole scale | $C_6H_5C{\equiv}CCCH_3(OC_2H_5)_2$[b] | 34.0 | 77.0<br>(76.8) | 8.3<br>(8.3) | 92 (3) | 1.5115 |
| $C_6H_5C{\equiv}CH$ | $n$-$C_4H_9C(OCH_3)_3$ | Methanol removed in 3.0 hr; $ZnI_2/ZnCl_2$ catalyst; 0.15 mole scale | $C_6H_5C{\equiv}CC_4H_7(OCH_3)_2$[c] | 40.0 | | | 121–124 (5) | 1.5339 |
| $C_6H_{11}CH_2C{\equiv}CH$[d] | $HC(OC_2H_5)_3$ | Ethyl alcohol removed in 1.8 hr; $ZnI_2/ZnCl_2$ catalyst; 0.18 mole scale | $C_6H_{11}CH_2C{\equiv}CCH(OEt)_2$[d] | 54.0 | 75.1<br>(75.1) | 10.7<br>(10.8) | 98–100 (3) | 1.4623 |
| $C_6H_5C{\equiv}CH$ | $C(OC_2H_5)_4$ | Ethyl alcohol removed in 1.8 hr; $ZnCl_2$ catalyst; 0.2 mole scale | $C_6H_5C{\equiv}CCH(OC_2H_5)_2$ | 14.2 | 72.6<br>(71.9) | 8.1<br>(8.3) | 126 (5) | 1.5004 |

[a] Infrared spectra, obtained for all products, were consistent with the structures as written. Absorption for internal $-C{\equiv}C-$ at 4.45 or 4.50 $\mu$, and for ether $-C{-}O-$ in the 9 $\mu$ region was noted. [b] This ketal was converted into the 2,4-dinitrophenylhydrazone of the corresponding ketone, m.p. 195°–198°C. *Anal.* Calcd. for $C_{16}H_{12}N_4O_4$: C, 59.3; H, 3.7; N, 17.3. Found: C, 59.3; H, 3.9; N, 17.0. [c] This ketal was converted into the 2,4-dinitrophenylhydrazone of the corresponding ketone, m.p. 130°–131°C. *Anal.* Calcd. for $C_{19}H_{18}N_4O_4$: C, 62.4; H, 4.9; N, 15.3. Found: C, 62.1; H, 5.0; N, 15.1. [d] $C_6H_{11}$ = cyclohexyl. [Reprinted from B. W. Howk and J. C. Sauer, *J. Amer. Chem. Soc.* **80**, 4607 (1958). Copyright 1958 by the American Chemical Society. Reprinted by permission of the copyright owner.]

of phenylacetylene, and 3.0 gm of zinc iodide* catalyst. The flask must first be heated to 135°C before ethanol starts to reflux. The ethanol distillate (26.4 gm) boiling at 65°–88°C is removed over a period of 1 hr while the temperature of the reaction mixture is raised to 200°–210°C. The reaction mixture is cooled and filtered, the precipitate washed with 5 ml of ether and the ether combined with the filtrate is distilled to afford 73–80 gm (72–78%), b.p. 99–100°C (2.0 mm Hg), $n_D^{25}$ 1.5153–1.5158. The IR spectrum showed absorption at 4.5-$\mu$ ($-C{\equiv}C-$) and 9.0-$\mu$ region ($-C{-}O$).

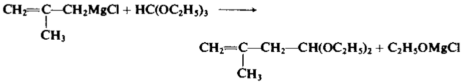
## H. Reaction of Orthoformate Esters with Grignard Reagents

Bodroux [89a,b] and Tschitschibabin [90a,b] earlier reported that Grignard reagents react with ortho esters to give the acetal, which upon hydrolysis gives the aldehyde (Eq. 68).

$$RMgX + HC(OC_2H_5)_3 \xrightarrow{\text{ether}} RCH(OC_2H_5)_2 \xrightarrow{H_3O^+} RCH{=}O \qquad (68)$$

Tschitschibabin [90a,b] and later investigators [91a–e] found that the maximum yield of acetal is obtained by refluxing equimolar amounts of the Grignard and the triethyl orthoformate or allowing them to stand for 15–24 hr. The yields usually are in the 80–90% range [92]. This procedure has been extended to the preparation of substituted acetals containing olefinic [93], acetylenic [94], and ketonic groups [95]. Some examples illustrating the utility of this method are shown in Table XIX and in Preparations 2-25 to 2-27.

### *2-25. Preparation of the Diethyl Acetal of 3-Methyl-3-buten-1-al* [93]



$$CH_2{=}\underset{\overset{|}{CH_3}}{C}{-}CH_2MgCl + HC(OC_2H_5)_3 \longrightarrow CH_2{=}\underset{\overset{|}{CH_3}}{C}{-}CH_2{-}CH(OC_2H_5)_2 + C_2H_5OMgCl \qquad (69)$$

To a flask containing 22.8 gm (0.20 mole) of methallyl magnesium chloride (prepared from 0.2 mole of methallyl chloride and 0.2 mole magnesium) is added dropwise 25 gm (0.17 mole) of triethyl orthoformate and the solution is refluxed for $6\frac{1}{2}$ hr. Half of the ether is removed under reduced pressure and to the remaining ether solution is added ice water. The ether layer is separated, dried, and distilled to afford 5.9 gm (24%), b.p. 154–155°C (760 mmHg), $n_D^{20}$ 1.4098; *p*-nitrophenylhydrazone, m.p. 157°C.

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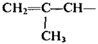
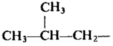
* An equivalent amount of zinc nitrate may be substituted for zinc iodide without lowering the yield of product. However, the use of anhydrous zinc chloride requires 2–3 hr heating and gives only 64–70% yield of product.

## TABLE XIX

### Preparation of Acetals by the Reaction of Grignard Reagents with Ortho Esters

| RMgX, X = Br R = (moles) | $CH(OR)_3$ (moles) | Solvent, ether (ml) | Reaction conditions Temp. (°C) | Reaction conditions Time (hr) | Yield (%) | B.p., °C (mm Hg) | $n_D$ (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|
|  $CH_2{=}C(CH_3){-}CH{-}$<br>(0.2) | $CH(OC_2H_5)_3$<br>0.17 | 100 | 35 | 6½ | 24 | 154–155<br>(760) | 1.4098<br>(20) | *a* |
| $n$-$C_4H_9$—<br>(2.0) | 2.0 | 300 | 35 | 16 | 80 | 143–144<br>(760) | — | *b* |
|  $CH_3{-}CH(CH_3){-}CH_2{-}$<br>(2.0) | 2.0 | 300 | 35 | 16 | 83 | 133–136<br>(760) | — | *b* |
| $(CH_3)_2CH{-}CH_2CH_2{-}$<br>(2.0) | 2.0 | 300 | 35 | 16 | 90 | 156–158<br>(760) | — | *b* |
| $n$-$C_4H_9$—<br>(0.3) | $CH(OC_2H_5)_2OC_6H_5$<br>0.3 | 150–200 | 35 | 1–2 | 91 | 50 (9) | 1.4025<br>(20) | *c* |
| $C_6H_5$—<br>(0.215) | 0.215 | 150–200 | 35 | 1–2 | 89 | 89–90<br>(9) | 1.4795<br>(20) | *c* |

[a] D. Kritchevsky, *J. Amer. Chem. Soc.* **65**, 487 (1943). [b] S. M. McElvain, R. L. Clarke, and G. D. Jones, *J. Amer. Chem. Soc.* **64**, 1966 (1942). [c] H. Stetter and E. Reske, *Chem. Ber.* **103**, 643 (1970).

### *2-26. Preparation of* n-*Butyraldehyde Diethyl Acetal* [92]

$$n\text{-}C_4H_9Br + Mg \longrightarrow n\text{-}C_4H_9MgBr \xrightarrow{CH(OC_2H_5)_3} n\text{-}C_4H_9CH(OC_2H_5)_2 + C_2H_5OMgBr \quad (70)$$

To a three-necked flask equipped with an air-tight mechanical stirrer, dropping funnel, reflux condenser, and drying tube, are added 3.0 gm (1.25 gm-atom) magnesium turnings, 50 ml of dry ether, and a small crystal of iodine. Then 5 gm of *n*-butyl bromide is added dropwise until 171.0 gm (1.25 mole) has been added. The reaction takes about $\frac{1}{2} - 1$ hr if the reaction mixture is cooled. The solution is refluxed for $\frac{1}{2}$ hr, cooled to 50°C, and then 148 gm (1.0 mole) of triethyl orthoformate is added dropwise over a $\frac{1}{2}$-hr period. The reaction mixture is refluxed for 16 hr, crushed ice added to decompose the excess Grignard reagent, the ether separated and washed with water. The water layer is added to a separatory funnel containing 200 ml of ether, treated with acetic acid to pH 7.0, shaken, and the ether separated. The latter ether layer is washed with 10% aqueous sodium carbonate, water, and dried. The latter water layer is extracted twice again with ether (200 ml). The combined ether layers are dried over potassium carbonate and fractionated to afford 128 gm (80%), b.p. 143°–144°C.

Recently Stetter and Reske [96] reported that Grignard reagents react under mild conditions with diethyl phenyl orthoformate to give acetals in high yields. Whether this ortho ester consistently gives superior results to triethyl orthoformate is still to be ascertained.

$$RMgBr + C_6H_5OCH(OC_2H_5)_2 \longrightarrow RCH(OC_2H_5)_2 + C_6H_5OMgBr \quad (71)$$

$$R = n\text{-}C_4H_9 \text{ or } C_6H_5$$

### *2-27. Preparation of Pentanal Diethyl Acetal* [96a]

$$C_4H_9MgBr + C_6H_5O{-}CH(OC_2H_5)_2 \longrightarrow C_4H_9CH(OC_2H_5)_2 + C_6H_5OMgBr \quad (72)$$

To a flask equipped as in Preparation 2-23 and containing 137.5 ml (0.3 mole) of etheral *n*-butylmagnesium bromide is added dropwise 58.9 gm (0.3 mole) of diethyl phenyl orthoformate dissolved in 120 ml of ether. The reaction is exothermic and causes the ether to reflux and precipitate a colorless precipitate. The reaction mixture is refluxed for $\frac{1}{2}$ hr, added to 30% aqueous ammonium chloride, extracted with 200 ml of ether, washed with water, dried, and distilled to afford 43.5 gm (90.5%), b.p. 50°C (9 mm Hg), $n_D^{20}$ 1.4025.

A modified Reformatsky [19a,b] reaction can also be used in a similar fashion. In this case $\alpha$-bromo esters are reacted with triethyl orthoformate

TABLE XX

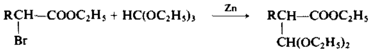
PREPARATION OF ACETALS BY THE REACTION OF α-BROMO ESTERS WITH TRIETHYL ORTHOFORMATE IN THE PRESENCE OF ZINC METAL[a]

| α-Bromo esters (moles) | | Yield (%) | B.p., °C (20 mm Hg) |
|---|---|---|---|
| *Ethyl propionate* (0.2) | $HC(OC_2H_5)_3$, 0.24 moles; Zn[b], 1.53 gm-atom<br>*Solvent:* 100 ml benzene<br>*Reaction conditions:* 80°C, ¾ hr | 44 | *99–102* |
| Ethyl isobutyrate (0.2) | | 59 | 104–107 |
| Ethyl *n*-caproate (0.2) | | 47 | 132–136 |
| Ethyl hexahydrobenzoate (0.2) | | 53 | 149–152 |

[a] Data taken from N. C. Deno, *J. Amer. Chem. Soc.* **69**, 2233 (1947).

[b] Granulated zinc is washed with dilute HCl, rinsed with water, methanol, acetone, and dried at 100°C and 20 mm for 10 min prior to use. A crystal of iodine is added as an activating agent.

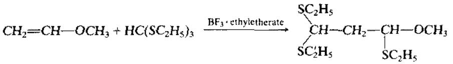
in the presence of zinc to give the diethyl acetal of the α-formyl ester (Eq. 73). Several examples of this method are shown in Table XX.



$$\underset{\displaystyle Br}{RCH}\text{—}COOC_2H_5 + HC(OC_2H_5)_3 \xrightarrow{Zn} \underset{\displaystyle CH(OC_2H_5)_2}{RCH}\text{—}COOC_2H_5 \qquad (73)$$

## I. Reaction of Trithioorthoesters with Vinyl Ethers

The reaction of methyl vinyl ether with ethyl trithioorthoformate in the presence of boron trifluoride diethylether complex has earlier been reported to give 1,methoxy-1,3,3-trithioethyl propane (a thioacetal) [96b].



$$CH_2{=}CH\text{—}OCH_3 + HC(SC_2H_5)_3 \xrightarrow{BF_3\cdot \text{ethyletherate}} (SC_2H_5)_2CH\text{—}CH_2\text{—}\underset{\displaystyle SC_2H_5}{CH}\text{—}OCH_3 \qquad (74)$$

## J. Reaction of Dihalomethylene Compounds with Sodium Alkoxides

Several dihalomethylene compounds react with sodium alkoxides to give acetals (Eq. 75) [98a,b]. For example, methylene, alkoxy 1,1-dihalocyclopropanes, dichloroacetic acid, and vinylidene chloride react with sodium or potassium alkoxides to give the corresponding substituted acetals in fair to good yields.

$$(R)_2CX_2 + 2NaOR' \longrightarrow (R)_2C(OR')_2 + 2NaX \qquad (75)$$

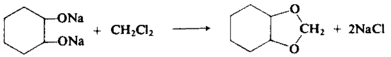
Several examples illustrating the utility of this reaction are summarized in Table XXI and in Procedures 2-28 to 2-30.

Ketene acetals are easily obtained by the above method by reacting vinylidene chloride with 2 moles of sodium alcoholates in diethylene glycol dimethyl ether as the solvent (Eq. 76). The use of alcohols as the solvent leads to ortho ester derivatives. This method has merit in that vinylidene chloride is commercially available and is an inexpensive starting material for the preparation of ketene acetals.

$$CH_2{=}CCl_2 + 2RONa \xrightarrow{-NaCl} CH_2{=}C(OR)_2 \xrightarrow{ROH} CH_3{-}C(OR)_3 \qquad (76)$$

The preparation of ketene acetals by the dehydrohalogenation [98c,d] of haloacetals is described in Section 3.C.

### *2-28. Preparation of* cis-*Hexahydro-1,3-benzodioxolane* [99]



(77)

To a flask containing 22.7 gm (0.20 mole) of cyclohexane-*cis*-1,2-diol in 125 ml of dimethylformamide is added portionwise 15.3 gm (0.64 mole) of sodium hydride over a 45 min period while keeping the temperature at 0°C. The reaction is stirred for 3 hr more and then 53 gm (0.62 mole) of methylene chloride is added dropwise over a 4-hr period while keeping the temperature at 30°C. The reaction mixture is stirred an additional 32 hr and then another 20 gm (0.24 mole) of methylene chloride and 6.3 gm (0.26 mole) of sodium are added. The reaction mixture is cooled to 0°C, methanol (25 ml) is added dropwise to destroy the excess sodium hydride, and then after 3 hr 250 ml water is added. The solution is continuously extracted with petroleum ether over an 18 hr period, the extract dried, concentrated, and the residue distilled to afford 11.6 gm (46%), b.p. 56°–57°C (15 mm Hg), $n_D^{21}$ 1.4598.

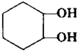
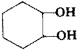
### *2-29. Preparation of Ketene Di(2-methoxyethyl) Acetal* [100]

$$2CH_3OCH_2CH_2ONa + H_2C{=}CCl_2 \longrightarrow H_2C{=}C(OCH_2CH_2OCH_3)_2 + 2NaCl \qquad (78)$$

To a flask containing a solution of 304 gm (4.0 mole) of 2-methoxyethanol (Methyl Cellosolve) in 500 gm of diethylene glycol dimethyl ether

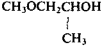
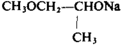
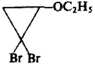
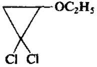
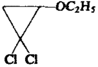
## TABLE XXI

### PREPARATION OF ACETALS BY THE REACTION OF DIHALOMETHYLENE COMPOUNDS WITH SODIUM ALKOXIDES

| $(R)_2CCl_2$ (moles) | ROH (moles) | NaOR (moles) | Base (moles) | Solvent (ml) | Reaction conditions |  | Yield (%) | B.p., °C (mm Hg) | $n_D$ (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  |  | Temp. (°C) | Time (hr) |  |  |  |  |
| $CHCl_2$<br>(0.63) | <br>*cis*<br>(0.20) | — | NaH<br>(0.64) | DMF<br>(125) | 0–30 | 7–8 | 46 | 56–57<br>(15) | 1.4598<br>(21) | *a* |
| $CH_2Br_2$<br>(0.52) | <br>*trans*<br>(0.26) | — | NaH<br>(0.46) | DMF<br>(350) | 25 | 62 | 17 | 50–51<br>(15) | 1.4751<br>(20) | *a* |
| $Cl_2COOH$<br>(0.39) | — | $NaOC_2H_5$<br>(1.35) | — | $C_2H_5OH$<br>(400) | 78 | 4 | 45–50 | 81–83<br>(12) | 1.4075<br>(25) | *b* |
| $CH_2{=}CCl_2$<br>(2.51) | — | $CH_3OCH_2CH_2ONa$<br>(4.0) | — | Diethylene glycol dimethyl ether<br>(500) | 130–170 | 2–3 | 51 | 78–80<br>(2.0) | — | *c* |

(*continues*)

TABLE XXI (continued)

| $(R)_2CCl_2$ (moles) | ROH (moles) | NaOR (moles) | Base (moles) | Solvent (ml) | Reaction conditions | | Yield (%) | B.p., °C (mm Hg) | $n_D$ (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Temp. (°C) | Time (hr) | | | | |
| $CH_2{=}CCl_2$<br>*(3.10)* |  $CH_3OCH_2\underset{CH_3}{\underset{\vert}{C}}HOH$<br>(6.75) |  $CH_3OCH_2{-}\underset{CH_3}{\underset{\vert}{C}}HONa$<br>(4.35) | — | — | 90-100 | 2-3 | 47 | 58-59<br>*(3.0)* | — | *c* |
|  <br>*(0.2)* | $(CH_3)_3COH$<br>(0.2) | — | — | — | 82-83 | 2 | 53 | 48-50<br>(10) | 1.4280<br>(21) | *d* |
|  <br>(0.16) | $(CH_3)_3COH$<br>(1.1) | $(CH_3)_3COK$<br>(0.19) | — | — | 82-83 | 12 | 73 | 40-42<br>(10) | 1.4277<br>(22) | *d* |
|  <br>(0.1) | $C_2H_5OH$<br>(1.0) | $C_2H_5ONa$<br>(0.13) | — | — | 78 | 48 | 75 | 78 (25) | 1.4262<br>(24) | *e* |

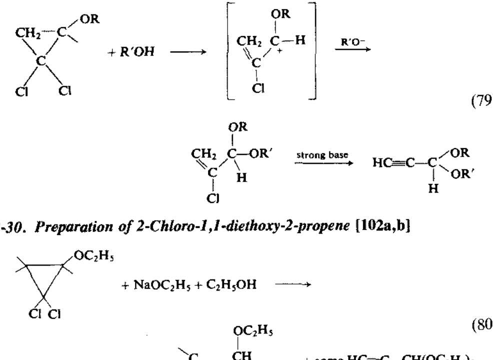
---

[a] J. S. Brimacombe, A. B. Foster, B. D. Jones, and J. J. Willard, *J. Chem. Soc. C* 2404 (1967). [b] R. B. Moffett, *Org. Syn. Coll.* **4**, 427 (1963); T. B. Johnson and L. H. Cretcher, Jr., *J. Amer. Chem. Soc.* **37**, 2144 (1915); A. Wohl and M. Lange, *Ber.* **41**, 3612 (1908). [c] W. C. Kuryla and D. G. Leis, *J. Org. Chem.* **29**, 2773 (1964); W. C. Kuryla and J. E. Hyre, *Org. Syn.* **47**, (1967). [d] $HC{\equiv}C{-}CH(OC_2H_5)\,O\text{-}t\text{-}C_4H_9$. L. Skattebøl, *J. Org. Chem.* **31**, 1554 (1966). [e] $CH_2{=}CCl{-}CH(OC_2H_5)_2$. L. Skattebøl, *J. Org. Chem.* **31**, 1554 (1966).

(see Note (d)) in a nitrogen atmosphere is added portionwise 92.0 gm (4.0 gm-atom) of sodium metal while keeping the temperature at 100°–130°C. After the sodium metal is reacted (Note (b)) heating is discontinued and 243 gm (2.5 moles) of 1,1-dichloroethene (vinylidene chloride) is added dropwise at such a rate that the temperature remains between 130° and 170°C. The resulting sodium chloride is filtered, washed with ether in order to remove the color, and dried to afford 225 gm (96%). The combined ether washings and filtrate are distilled under reduced pressure to afford 181 gm (51%) (Note (c)), b.p. 81°–84°C (2 mm Hg), $n_D^{25}$ 1.4411.

NOTES: (a) Xylene (100 ml) may be used as a solvent with good results in place of diethylene glycol dimethyl ether. (b) Approximately 20–25 gm more of 2-methoxyethanol may have to be added to consume the small amounts of unreacted sodium metal. (c) Yields ranging from 56 to 75% have been reported [101].

The 1,1-dihalocyclopropyl ether ring open with either alkoxides or with pyridine in alcohol to give acetals as shown in Eq. (66) and in Table XXII.



(79)

### 2-30. *Preparation of 2-Chloro-1,1-diethoxy-2-propene* [102a,b]

(80)

To a flask containing 50 ml of absolute ethanol is added portionwise 3.0 gm (0.13 gm-atom) of sodium metal. After the reaction is complete

## TABLE XXII

### REACTION OF 1,1-DICHLOROCYCLOPROPANES WITH ALCOHOLIC BASE TO GIVE ALLYLIC ACETALS

| Cyclopropane derivative | Base | Solvent | Product | Yield (%) |
|---|---|---|---|---|
| 1,1-Dichloro-2-ethoxy | $KOC_4H_9$-*t* | *t*-$C_4H_9OH$ | $HC{\equiv}C{-}CH(OC_2H_5)OC_4H_9$-*t* | 73 |
| | $NaOC_2H_5$ | $C_2H_5OH$ | $CH_2{=}CCl{-}CH(OC_2H_5)_2{}^a$ | 89 |
| | Pyridine | $C_2H_5OH$ | $CH_2{=}CCl{-}CH(OC_2H_5)_2{}^a$ | 75 |
| *trans*-1,1-Dichloro-2-ethoxy-3-methyl | $NaOC_2H_5$ | $C_2H_5OH$ | *trans*-$CH_3CH{=}CCl{-}CH(OC_2H_5)_2$ | 90 |
| *trans*-1,1-Dichloro-2-ethoxy-3-methyl | Pyridine | $C_2H_5OH$ | *trans*-$CH_3CH{=}CCl{-}CH(OC_2H_5)_2$ | 81 |
| *cis*-1,1-Dichloro-2-ethoxy-3-methyl | Pyridine | $C_2H_5OH$ | *trans*-$CH_3CH{=}CCl{-}CH(OC_2H_5)_2$ | 83 |
| 1,1-Dichloro-2-ethoxy-3,3-dimethyl | $KOC_4H_9$-*t* | *t*-$C_4H_9OH$ | $(CH_3)_2C{=}CCl{-}CH(OC_2H_5)OC_4H_9$-*t* | 69 |
| | $NaOC_2H_5$ | $C_2H_5OH$ | $(CH_3)_2C{=}CCl{-}CH(OC_2H_5)_2$ | 86 |
| | Pyridine | $C_2H_5OH$ | $(CH_3)_2C{=}CCl{-}CH(OC_2H_5)_2$ | 82 |
| | $K_2CO_3$ | $C_2H_5OH$ | $(CH_3)_2C{=}CCl{-}CH(OC_2H_5)_2$ | 72 |
| | $NaOCH_3$ | Dioxane | $(CH_3)_2C{=}CCl{-}CN(OC_2H_5)OCH_3$ | 77 |
| 1,1-Dichloro-2-ethoxy-2-methyl | $NaOC_2H_5$ | $C_2H_5OH$ | $HC{\equiv}C{-}C(OC_2H_5)_2CH_3$ | 50 |
| | | | $HC{\equiv}C{-}C(OC_2H_5){=}CH_2$ | 15 |

[a] A small amount of the acetylenic acetal was also formed. [b] A mixture of stereoisomers. [Reprinted in part from L. Skattebøl, *J. Org. Chem.* 31, 1554 (1966). Copyright 1966 by the American Chemical Society. Reprinted by permission of the copyright owners.]

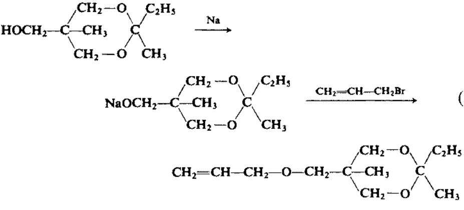
15.5 gm (0.1 mole) of 1,1-dichloro-2-ethoxycyclopropane is added and the mixture heated to reflux for 48 hr. Some of the ethanol is removed by distillation at reduced pressure and then a 5% aqueous sodium carbonate solution is added to the residue. The acetal is extracted with ether, the ether is dried, concentrated, and the residue fractionated to afford 12.4 gm (75%), b.p. 70°–78°C (25 mm Hg), $n_D^{24}$ 1.4210–1.4293. The acetal is contaminated with the corresponding acetylenic acetal and therefrom is refractionated to give the pure acetal, b.p. 78°C (25 mm), $n_D^{24}$ 1.4262. Using pyridine in place of sodium ethoxide affords the pure acetal in 89% yield. The use of potassium *t*-butoxide in *t*-butanol in place of sodium ethoxide affords only 1-*t*-butoxy-1-ethoxy-2-propyne in 73% yield.

## 3. REACTIONS OF ACETAL AND KETAL COMPOUNDS

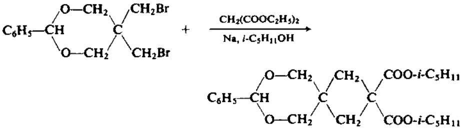
Acetal and ketals can undergo most of the functional group reactions on their side chains as long as the reactions are carried out at neutral or basic conditions. For example, olefinic groups can be halogenated or oxidized. Halogen groups, depending on their position, can be condensed with other compounds or can be eliminated to give an olefinic group. Very important reactions are the transacetalization and transketalization reactions, wherein existing alkoxy groups are exchanged for others, usually by reacting with higher-boiling alcohols.

### A. Condensation Reactions of Halo Acetals, Hydroxy Acetals, and Olefinic Acetals

The side chain attached to the acetal functional group is capable of undergoing the ordinary condensation reactions. For example, hydroxymethyl groups may be reacted further to give esters or ethers (Eq. 81) [103]. Haloaklyl groups may be condensed further as with malonates to give substituted malonic esters [104]. The compound shown in Eq. (82) is useful.



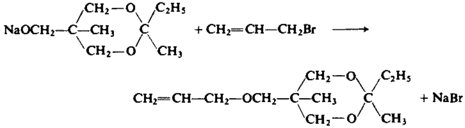
(81)


(82)

In addition, halogen groups on acetals react with Grignard reagents as shown in Eq. (83) [105].

$$C_6H_5—MgX + Cl—C{\equiv}C—CH(OC_2H_5)_2 \longrightarrow C_6H_5—C{\equiv}C—CH(OC_2H_5)_2 + MgXCl \qquad (83)$$

### *3-1. Preparation of 2-Methyl-3-ethyl-5-allyloxymethyl-5-methyl-1,3-dioxane* [103]


(84)

To a flask containing 698 gm (3.52 moles) of the sodium salt of 2.5-dimethyl-2-ethyl-5-hydroxymethyl-1,3-dioxane (see Note) in 400 ml of toluene is added dropwise over a 25-min period 445 gm (3.67 moles) of allyl bromide while keeping the reaction temperature between 119° and 127°C. The reaction mixture is refluxed for 1 hr, cooled to 50°C, 500 ml of water added, the toluene layer separated, dried, and distilled to afford 760 gm (88%), b.p. 113° (14 mmHg), $n_D^{25}$ 1.4452.

NOTE: Prepared by reaction of sodium metal on the hydroxy ketal in ketone.

The haloalkyl groups may also be hydrolyzed to alcohols as reported for 2-(2-chloroethyl)-4,4,6-trimethyl-1,3-dioxane [106]. In addition, a recently reported procedure for the preparation of diethyl mercaptoacetal involves the reaction of diethyl bromoacetal with sodium sulfide as shown in Eq. (85) [107].

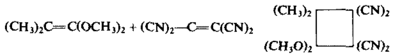
$$2BrCH_2CH(OC_2H_5)_2 + Na_2S_3 \xrightarrow[H_2O]{C_2H_5OH}$$

$$[(C_2H_5O)_2CH—CH_2]_2S \xrightarrow[2.\ NH_4Cl,\ HCl,\ CO_2]{1.\ Na/NH_3} HSCH_2CH(OC_2H_5)_2 \qquad (85)$$

Unsaturated groups on acetals also undergo cycloaddition reactions [108] and reaction with diazo esters [109].

Ester groups on acetals react without complication with Grignard reagents [110].

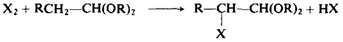
### 3-2. *Preparation of 3,3-Dimethoxy-4,4-dimethyl-1,1,2,2-cyclobutanetetracarbonitrile* [111]

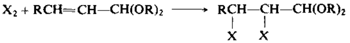

(85a)

To a flask containing 3.2 gm (0.025 mole) of ethenetetracarbonitrile (tetracyanoethylene) in 25 ml of acetonitrile at 25°C is added dropwise over a 5 min period 4.4 gm (0.038 mole) of dimethylketene dimethyl acetal. The temperature rises to 38°C and then drops to room temperature. The solvent is removed under reduced pressure and the solid residue is recrystallized from acetonehexane to afford 5.2 gm (85%), m.p. 136°–137°C.

## B. Halogenation Reactions

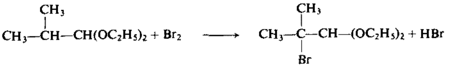
Acetal and ketals undergo bromination or chlorination of the backbone to give α-halo derivatives or dihalo derivatives as shown in Table XXIII and Eqs. (86 and 87).


$$X_2 + RCH_2{-}CH(OR)_2 \longrightarrow R{-}\underset{X}{\underset{|}{CH}}{-}CH(OR)_2 + HX \qquad (86)$$


$$X_2 + RCH{=}CH{-}CH(OR)_2 \longrightarrow R\underset{X}{\underset{|}{CH}}{-}\underset{X}{\underset{|}{CH}}{-}CH(OR)_2 \qquad (87)$$

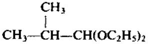
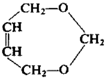
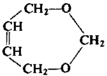
Hydrogen bromide can also be added to unsaturated acetals [112]. Thus the olefinic group should be capable of undergoing the typical reactions described in Chapter 2 of Volume I of this text [113].

### 3-3. *Preparation of α-Bromoisobutyraldehyde Diethyl Acetal* [114]


$$CH_3{-}\overset{CH_3}{\overset{|}{CH}}{-}CH(OC_2H_5)_2 + Br_2 \longrightarrow CH_3{-}\underset{Br}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}{-}CH{-}(OC_2H_5)_2 + HBr \qquad (88)$$

## TABLE XXIII

### HALOGENATION OF SATURATED AND UNSATURATED ACETALS

| Acetal (moles) | Halogen (moles) | Solvent (ml) | Reaction conditions Temp. (°C) | Reaction conditions Time (hr) | Yield (%) | B.p., °C (mm Hg) or m.p., °C | Ref. |
|---|---|---|---|---|---|---|---|
|  $CH_3-\overset{CH_3}{CH}-CH(OC_2H_5)_2$<br>(0.5) | $Br_2$<br>(0.51) | $CHCl_3$<br>(200) | 61–62 | 1–2 | 48 | 89 (18) | *a* |
| $CH_3CH(OC_2H_5)_2$<br>(1.0) | $Br_2$<br>(1.0) | $(CaCO_3)$<br>55 gm | 10 | ½–1 | 31–42 | 167–170 | *b* |
| <br>(1.0) | $Br_2$<br>(0.875) | $CHCl_3$<br>(700) | −55 | 3 | 100 | 39–40 | *b* |
| <br>(1.17) | $Cl_2$<br>(1.17) | $CHCl_3$<br>(700) | −55 | 2 | 75 | 56 (1) | *b* |

---

[a] F. M. Hamer and R. J. Rathbone, *J. Chem. Soc.* 597 (1945).

[b] W. H. Hartung and H. Adkins, *J. Amer. Chem. Soc.* **49**, 2517 (1927).

[c] D. B. Pattison, *J. Org. Chem.* **22**, 662 (1957).

To a flask containing 73 gm (0.5 mole) of isobutyraldehyde diethyl acetal dissolved in 200 ml of chloroform and 50 gm (0.5 mole) of calcium carbonate is added dropwise 28 ml (0.51 mole) of bromine at such a rate to keep the reaction mixture gently boiling. After the addition, the reaction mixture is cooled, 200 ml of water added, filtered, the chloroform layer washed with water and dried over potassium carbonate. The chloroform solvent is removed under reduced pressure and the residue is distilled to afford 53.7 gm (48%), b.p. 89°C (18 mm Hg).

### *3-4. Preparation of Bromoacetaldehyde Diethyl Acetal* [115a]

$$\mathrm{CH_3CH(OC_2H_5)_2 + Br_2 \longrightarrow Br{-}CH_2CH(OC_2H_5)_2 + HBr} \tag{89}$$

To a flask containing 118.0 gm (1.0 mole) of diethyl acetal and 55 gm (0.55 mole) of calcium carbonate is dropwise added 55 ml (1.0 mole) of bromine over a 30–45 min period while keeping the reaction temperature at 5°–10°C. The reaction mixture is allowed to stand 24 hr, steam is introduced to dissolve the salts, the oil separated, dried over potassium carbonate, and distilled to afford 61–83 gm (31–42%), b.p. 167°–170°C. The product is further purified by shaking with potassium carbonate and distilling it under reduced pressure, b.p. 48°–49°C (3 mm Hg), $d_4^{25}$ 1.28. The pure acetal is unstable and becomes colored in a few hours and black after several days. However, the crude acetal boiling at 167°–170°C is stable for several months. The bromo acetal is a strong lachrymator.

The latter bromo acetal can be converted to the cyano acetal, hydroxy acetal, or amino acetal by reacting, respectively, with potassium cyanide, potassium hydroxide, or alcoholic ammonia [115a].

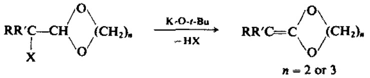
Recently the bromination of 6,8-dioxabicyclo[3.2.1]octane has been reported to give an 80% yield of *cis*- and *trans*(2:3)-4-bromo-6,8-dioxabicyclo-[3.2.1]octane [115b].

## C. Dehydrohalogenation Reactions

Acetal side chains undergo dehydrohalogenation to give vinyl groups. For example, β-chloropropionaldehyde acetal, on reaction with powdered potassium hydroxide, affords a 75% yield of acrolein acetal (Eq. 90) [116].

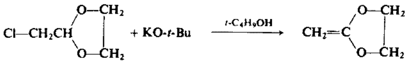
$$\mathrm{KOH + Cl{-}CH_2CH_2CH(OC_2H_5)_2 \longrightarrow CH_2{=}CH{-}CH(OC_2H_5)_2 + KCl + H_2O} \tag{90}$$

Ketene acetals can be obtained in 50–80% yields by the dehydrohalogenation of the corresponding halogenated cyclic ketals using potassium *t*-butoxide in butyl alcohol (Eq. 91) [117].



(91)

### *3-5. Preparation of 2-Methylene-1,3-dioxolane* [117]



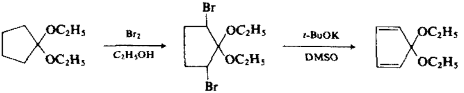
(92)

To a flask containing 61.3 gm (0.50 mole) of 1-chloromethyl-1,3-dioxolane is added 73.2 gm (0.60 mole) of potassium *t*-butoxide dissolved in 150 ml of *t*-butyl alcohol and the reaction is refluxed for 1–2 hr. A more accurate time can be obtained by checking the vapor-phase chromatogram for disappearance of the starting material and appearance of product. The product is obtained by distillation in 22–34 gm (50–80%), b.p. 120°–124°C (735 mm Hg), $n_D^{25}$ 1.4465.

Several examples of related products that can be prepared by this procedure are shown in Table XXIV.

Some halogenated cyclic side chains of acetals rearrange during dehydrogenation to nonacetal products. Chlorocyclopropyl acetals are thermally unstable and rearrange to unsaturated alkyl esters [118]. In addition, 2,6-dibromocyclohexanone ethylene ketal rearranges during dehalogenation to 2-hydroxyethyl phenyl ether [119].

Recent cyclopentadienone ethyl ketal has been reported to be prepared by a dehydrohalogenation reaction of the related dibromo ketal [120a].



(93)

## D. Transacetalization

The transacetalization reaction usually involves displacement of the existing alkoxy group by an alkoxy group of a higher boiling alcohol or mercaptan [120b,c]. The use of a lower-boiling alcohol gives mixed alkoxy groups as in the preparation of methyl ethyl acetal from diethyl acetal and methanolic HCl catalysis [121].

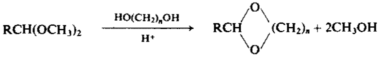
TABLE XXIV

2-METHYLENE-1,3-DIOXOLANES AND -1,3-DIOXANES AND SOME CORRESPONDING KETENE DIMETHYL ACETALS, $RR'C{=}\underline{CO(CH_2)_nO}$

| R | R′ | *n* | B.p., °C (mm Hg) | $n_D^{25}$ | Formula |
|---|---|---|---|---|---|
| H | H | 2 | 120–124 (735) | 1.4465 | $C_4H_6O_2$ |
| H | H | 3 | 147–155 (740) | 1.4304 | $C_5H_8O_2$ |
| $C_6H_5$ | H | 2 | 108–112 (0.8)[a] | 1.6075 | $C_{10}H_{10}O_2$ |
| $C_6H_5$ | H | 3 | 124–126 (0.6)[b] | 1.5840 | $C_{11}H_{12}O_2$ |
| Cl | H | 2 | 89–93 (23)[c] | 1.4874 | $C_4H_5ClO_2$ |
| Cl | H | 3 | 132–135 (23) | 1.4780 | $C_5H_7ClO_2$ |
| Br | H | 2 | 118–119 (24) | — | $C_4H_5BrO_2$ |
| Br | H | 3 | 73–75 (2) | 1.5007 | $C_5H_7BrO_2$ |
| Cl | Cl | 2 | 118–121 (21)[d] | — | $C_4H_4Cl_2O_2$ |
| Cl | Cl | 3 | 105–106 (8)[e] | — | $C_5H_6Cl_2O_2$ |
| | | | | | $RCH{=}C(OCH_3)_2$ |
| H | — | — | 89–91 (740)[f] | — | — |
| $C_6H_5$ | — | — | 81–82 (1.0)[g]<br>235–238 (735) | 1.5620 | $C_{10}H_{12}O_2$ |
| Cl | — | — | 740–141 (730) | 1.4460 | $C_4H_7ClO_2$ |
| Br | — | — | 171–172 (732) | 1.4880 | $C_4H_7BrO_2$ |

[a] M.p., 38°–40°C. [b] M.p., 25°–27°C. [c] This ketene acetal was completely polymerized within 2 hr. [d] M.p., 55.5°–57°C. [e] M.p., 67°–69°C. [f] B.p. reported by S. M. McElvain, H. I. Anthes, and S. H. Shapiro, *J. Amer. Chem. Soc.* **64**, 2525 (1942). [g] $d_4^{25}$, 1.0592; this material contained 36.6% methoxyl (calcd. 37.8); it was a colorless liquid in contrast to the pale yellow product, b.p. 240°–245°C, $n_D^{25}$ 1.5390, reported in S. M. McElvain and C. L. Stevens, *J. Amer. Chem. Soc.* **68**, 1917 (1946). [Reprinted from S. M. McElvain and M. J. Curry, *J. Amer. Chem. Soc.* **70**, 3781 (1948). Copyright 1948 by the American Chemical Society. Reprinted by permission of the copyright owner.]

The reaction of dimethyl or diethyl acetals with glycols or diols affords cyclic acetals [117, 112–124]. For example, ethylene glycol or 1,3-propanediol reacts with dimethyl or diethyl acetals as shown in Eq. (82) and the methanol or ethanol is removed by distillation [117].

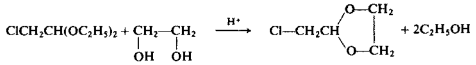


(94)

(75–90%)

$n = 2$ or 3

### *3-6. Preparation of 1-Chloromethyl-1,3-dioxolane* [117]



(95)

To a flask containing 152.5 gm (1.0 mole) of chloroacetaldehyde diethyl acetal is added 62.0 gm (1.0 mole) of ethylene glycol and 5 drops of concentrated sulfuric acid. The reaction is heated, the ethanol (92 gm) removed by distillation at 75–80°C, and the residue distilled in the presence of potassium carbonate to afford 92–111 gm (75–90%), b.p. 155°–159°C (740 mm Hg), $n_D^{25}$ 1.4465, $d_4^{24}$ 1.2337.

Other examples of cyclic acetals prepared by this method are shown in Table XXV (first nine examples).

TABLE XXV

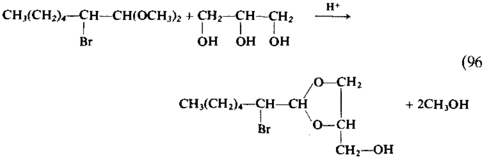
2-SUBSTITUTED-1,3-DIOXOLANES AND -1,3-DIOXANES, $RCHO(CH_2)_nO$[a]

| R | *n* | B.p., °C (mm Hg) | $n_D^{25}$ | $d_4^{25}$ | Formula |
|---|---|---|---|---|---|
| $CH_2Cl$ | 2 | 155–159 (740)[b] | 1.4465 | 1.2337 | — |
| $CH_2Cl$ | 3 | 67–69 (12)[c] | 1.4519 | 1.1893 | — |
| $CH_2Br$ | 2 | 172–175 (745)[d] | 1.4805 | 1.6358 | — |
| $C_6H_5CHBr$ | 2 | 162–165 (9)[e] | 1.5628 | — | $C_{10}H_{11}BrO_2$ |
| $C_6H_5CHBr$ | 3 | 120–125 (0.8)[f] | 1.5602 | — | $C_{11}H_{13}BrO_2$ |
| $CHCl_2$ | 2 | 186–188 (732)[g] | 1.4695 | 1.3861 | — |
| $CHCl_2$ | 3 | 210–212 (740) | 1.4796 | 1.3471 | $C_5H_8Cl_2O_2$ |
| $CHBr_2$ | 2 | 101–104 (9) | 1.5351 | 2.0617 | $C_4H_6Br_2O_2$ |
| $CHBr_2$ | 3 | 116–118 (9) | 1.5300 | 1.9345 | $C_5H_8Br_2O_2$ |
| $CCl_3$ | 2 | 198–200 (740)[h,i] | — | — | — |
| $CCl_3$ | 3 | 105–112 (12)[i,j] | — | — | $C_5H_7Cl_3O_2$ |

[a] The first nine acetals were obtained by Procedure 3-6 in 75–90% yields. The last two were obtained by the reaction of chloral (0.26 mole) with the glycol (0.26 mole) in the presence of 25 ml of sulfuric acid at 70°C. [b] M. Delépine, *C. R. Acad. Sci. Paris* **132**, 970 (1901). [c] E. G. Hallonquist and H. Hibbert, *Canad. J. Res.* **8**, 129 (1933). [d] M. M. Otto, *J. Amer. Chem. Soc.* **59**, 1590 (1937). [e] M.p., 37°C. [f] M.p., 46°–48°C. [g] F. P. A. Tellegen, *Rec. Trav. Chim.* **57**, 667 (1938). [h] M.p., 41°–42°C. [i] A. N. Meldrum and G. M. Vad, *J. Indian Chem. Soc.* **13**, 118 (1936). [j] M.p., 66.5°–68.5°C. [Adapted from S. M. McElvain and M. J. Curry, *J. Amer. Chem. Soc.* **70**, 3781 (1948). Copyright 1948 by The American Chemical Society. Reprinted by permission of the copyright owner.]

In a similar manner bromoalkyl dimethyl acetals have been reported to react with glycerol to afford 2(1'-bromoalkyl)-4-hydroxyethyl-1,3-dioxolanes.

### *3-7. Preparation of 2-(1'-Bromohexyl)-4-hydroxymethyl-1,3-dioxolane* [125]



(96)

To a flask equipped with a mechanical stirrer, Vigreux column, and distilling head is added 57.6 gm (0.63 mole) of glycerol, 74.8 gm (0.31 mole) of 2-bromo-1,1-dimethoxyheptane, and 0.075 gm of sulfosalicyclic acid. The reaction mixture is heated (oil bath 130°–140°C) slowly with stirring, the methanol (20.0 gm) is distilled and then the acidic catalyst neutralized with 30 ml of 5% potassium carbonate solution. The product is extracted with 200 ml of ether and the aqueous layer extracted twice with 200 ml of ether. The combined ether extracts are dried over sodium carbonate, concentrated, and the residue distilled to afford 65.4 gm (79%), b.p. 129°–133°C (0.95 mm Hg), $n_D^{31}$ 1.4798 (colorless liquid).

The compounds described in Table XXVI were prepared using the procedure of Preparation 3-7.

In a similar manner esters of ortho acids such as ethyl orthoformate react with glycerol to liberate 2 moles of ethanol by distillation and to leave behind a mixture of cis and trans isomers of both 2-ethoxy-1,3-dioxolane-4-methanol (88%) and 2-ethoxy-*m*-dioxan-4-ol (12%) [126].

Spirocyclic acetals can also be prepared by the alcoholysis reaction. For example, bis(2,5-dioxacyclopentyl)methane has been prepared in 81% yield by the reaction of ethylene glycol with 1,1,3,3-tetramethoxypropane (127a,b)

Another variation of transacetalization involves the acetal–acetal interchange reaction catalyzed by acid [127c]. For example:

$$2\,C_6H_{13}OCH_2OCH_3 \xrightarrow[\Delta \atop \text{(36 hr; toluene)}]{\text{PTSA}} C_6H_{13}OCH_2OC_6H_{13} + CH_3OCH_2OCH_3 \qquad (97)$$

TABLE XXVI

α-BROMO CYCLIC GLYCEROL ACETALS

| Compound | Molecular formula | B.p., °C (mm Hg) | $n_D^t$ | Temp. (°C) | Yield (%) |
|---|---|---|---|---|---|
| 2-(1′-Bromopropyl)-4-hydroxymethyl-1,3-dioxolane | $C_7H_{13}O_3Br$ | 105–107 (0.40) | 1.4939 | 23.8 | 47 |
| 2-(1′-Bromobutyl)-4-hydroxymethyl-1,3-dioxolane | $C_8H_{15}O_3Br$ | 106–109 (0.60) | 1.4849 | 23.5 | 80 |
| 2-(1′-Bromopentyl)-4-hydroxymethyl-1,3-dioxolane | $C_9H_{17}O_3Br$ | 125–130 (1.20) | 1.4755 | 34.0 | 68 |
| 2-(1′-Bromoheptyl)-4-hydroxymethyl-1,3-dioxolane | $C_{11}H_{21}O_3Br$ | 138–142 (0.75) | 1.4811 | 32.5 | 74 |
| 2-(1′-Bromooctyl)-4-hydroxymethyl-1,3-dioxolane | $C_{12}H_{23}O_3Br$ | 152–155 (1.00) | 1.4789 | 27.5 | 76 |
| 2-(1′-Bromononyl)-4-hydroxymethyl-1,3-dioxolane | $C_{13}H_{25}O_3Br$ | 155–160 (0.40) | 1.4810 | 22.0 | 73 |
| 2-(1′-Bromodecyl)-4-hydroxymethyl-1,3-dioxolane | $C_4H_{27}O_3Br$ | 156–157 (0.31) | 1.4790 | 32.0 | 72 |

[Reprinted from C. Piantadosi, A. F. Hirsch, C. L. Yarbro, and C. E. Anderson, *J. Org. Chem.* **28**, 2425 (1963). Copyright 1963 by The American Chemical Society. Reprinted by permission of the copyright owner.]

## E. Transketalization*

Ketals can also be formed from 2,2-dimethoxypropane by a ketal interchange reaction with primary [127a,b] and secondary alcohols (Eq. 98) [128a]. Mixed ketals are obtained when only 1 mole of alcohol is used per mole of 2.2-dimethoxypropane.

$$(CH_3)_2C(OCH_3)_2 + 2ROH \rightleftharpoons (CH_3)_2C(OR)_2 + 2CH_3OH \qquad (98)$$

Methyl ketals of other ketones are obtained by acidifying a mixture of the ketone and 2,2-dimethoxypropane, and removing the acetone by distillation [127]. The rate is faster when methanol is present since the reaction probably proceeds as in Eqs. (99 and 100).

$$R_2C{=}O + 2CH_3OH \rightleftharpoons R_2C(OCH_3)_2 + H_2O \qquad (99)$$

$$(CH_3)_2C(OCH_3)_2 + H_2O \rightleftharpoons 2CH_3OH + (CH_3)_2C{=}O \qquad (100)$$

Some transketalization reactions with 2,2-dimethoxypropane are summarized in Table XXVII.

---

* See also Section 2,F.

## TABLE XXVII

### TRANSKETALIZATION OF 2,2-DIMETHOXYPROPANE USING ALCOHOLS OR KETONES

| $(CH_3)_2C(OCH_3)$ (moles) | ROH (moles) | $R_2C{=}O$ (moles) | Catalyst, PTSA (ml) | Solvent (ml) | Reaction conditions | | Yield (%) | B.p., °C (mm Hg) | $n_D$ (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Temp. (°C) | Time (hr) | | | | |
| 3.00 | $C_4H_9OH$<br>(6.6) | — | 0.2 | $C_6H_6$<br>(1000) | 57–59 | 2–4 | 82 | 64<br>(2.3) | 1.4128<br>(20) | *a* |
| 2.40 | — | Cyclohexanone<br>(2.00) | 0.05 | $CH_3OH$<br>(200) | 58–63 | 2–4 | 95 | 80<br>(44) | 1.4390<br>(22) | *a* |
| 1.5 | *n*-$C_3H_7OH$<br>(8.00) | Acetophenone<br>(1.00) | 0.2 | Hexane<br>(300) | 50 | 4–5 | 63 | 61 (1) | 1.4750<br>(25) | *a* |
| 1.20 | *i*-$C_3H_7OH$<br>(4.40) | Cyclohexanone<br>(1.00) | 0.05 | $C_6H_6$<br>(250) | 34 | 24 | 57.5[c]<br>17[d] | 47–70<br>(8) | 1.4388<br>(24) | *b* |

[a] N. B. Lorette and W. L. Howard, *J. Org. Chem.* **25**, 521 (1960). [b] W. L. Howard and N. B. Lorette, *J. Org. Chem.* **25**, 525 (1960).
[c] Cyclohexanone isopropyl methyl ketal. [d] Cyclohexanone diisopropyl ketal.

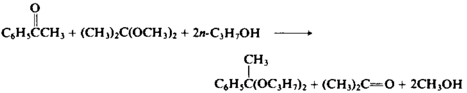
Recently the preparation 2,2(*p*-methoxyphenyl)-1,3-dioxolane has been reported to be obtained by the reaction of *p,p'*-dimethoxybenzophenone with ethylene glycol catalyzed by a trace of *p*-toluenesulfonic acid [128b].

Unsymmetrical ketals tend to disproportionate to a mixture of symmetrical ketals (Eq. 101) [127].

$$2(CH_3)_2C(OCH_3)(OR) \rightleftharpoons (CH_3)_2C(OCH_3)_2 + (CH_3)_2C(OR)_2 \qquad (101)$$

Mercuric oxide is reported to be a catalyst for the reaction of dithioacetals with alkyl alcohols to give dialkyl acetals [129].

### *3-8. Preparation of Acetophenone Dipropyl Ketal* [127]

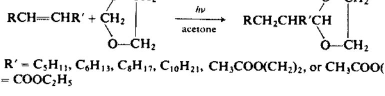


$$C_6H_5\overset{O}{\overset{\|}{C}}CH_3 + (CH_3)_2C(OCH_3)_2 + 2n\text{-}C_3H_7OH \longrightarrow C_6H_5\overset{CH_3}{\overset{|}{C}}(OC_3H_7)_2 + (CH_3)_2C{=}O + 2CH_3OH \qquad (102)$$

To a flask equipped with a mechanical stirrer, 1000 × 25 mm column packed with $\frac{1}{8}$ inch glass helices, and distillation head is added 120 gm (1.0 mole) of acetophenone, 480 gm (8.0 moles) of *n*-propyl alcohol, 156 gm (1.5 moles) of 2,2-dimethoxypropane, 300 ml of *n*-hexane, and 0.2 gm of *p*-toluenesulfonic acid. The reaction mixture is heated and the reflux ratio adjusted to keep the distillation head temperature below 50°C. After each 150–200 ml of distillate is collected an equal volume of *n*-hexane is added to the reaction mixture until 770 ml of distillate is collected. The catalyst is reacted with 0.2 gm of sodium methoxide in 10 ml of methanol and the distillation continued at atmospheric pressure or reduced pressure so that the pot temperature remains below 100°–110°C. The residue is distilled at reduced pressure to afford 139 gm (63%), b.p. 61°C (1.0 mm Hg), $n_D^{25}$ 1.4750.

## F. Photolytic Reactions

Recently acetals have been reported to be condensed, photolytically, with olefins [130]. The reactions are described in Eqs. (90) and (91) and some examples are shown in Tables XXVIII and XXIX.



(103)

R = H; R' = $C_5H_{11}$, $C_6H_{13}$, $C_8H_{17}$, $C_{10}H_{21}$, $CH_3COO(CH_2)_2$, or $CH_3COO(CH_2)_8$
R = R' = $COOC_2H_5$

## TABLE XXVIII

ADDITION PRODUCTS OF 1,3-DIOXOLANE AND OLEFINS[a] (INITIATED BY ACETONE)

| Olefin | 1:1 Addition products[b] (%) |
|---|---|
| 1-Heptene | 2-Heptyl-1,3-dioxolane, 28,[c] 35[d] |
|  | 4-Heptyl-1,3-dioxolane, 5[c] |
| 1-Octene | 2-Octyl-1,3-dioxolane, 25[c] |
|  | 4-Octyl-1,3-dioxolane, 2[c] |
| 1-Decene | 2-Decyl-1,3-dioxolane, 33,[c] 50[d] |
|  | 4-Decyl-1,3-dioxolane, 3,[c] 3[d] |
| 1-Dodecene | 2-Dodecyl-1,3-dioxolane, 35[c] |
|  | 4-Dodecyl-1,3-dioxolane, 6[c] |
| Methyl 4-pentenoate | Methyl 5-(1,3-dioxolanyl-2)-pentanoate, 18[e] |
|  | Methyl 5-(1,3-dioxolanyl-4)-pentanoate, 2[c] |
| Methyl 10-undecylenate | Methyl 11-(1,3-dioxolanyl-2)-undecanoate, 19[c] |
| Diethyl maleate | Diethyl (1,3-dioxolanyl-2)-succinate, 90[c] |

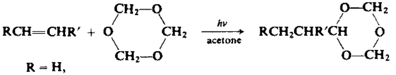
[a] The mole ratio of 1,3-dioxolan–olefin was 20:1 for terminal olefins and 70:1 for diethyl maleate. [b] Yields are based on the olefins employed. The consumptions were nearly quantitative in most cases. The ratio between isomers was determined by the intensity of corresponding peaks in glpc. [c] Hanau Q81 high-pressure mercury vapor lamps fitted into Pyrex tubes were used as the radiation source for these reactions. [d] In sunlight. [e] Initiated by acetophenone. [Reprinted from I. Rosenthal and D. Elad, *J. Org. Chem.*, **33**, 805 (1968). Copyright 1968 by The American Chemical Society. Reprinted by permission of the copyright owner.]

## TABLE XXIX

ADDITION PRODUCTS OF 1,3,5-TRIOXANE AND OLEFINS[a] (INITIATED BY ACETONE)

| Olefin | 1:1 Addition product[b] (%) |
|---|---|
| 1-Heptene | Heptyl-1,3,5-trioxane, 15[c] |
| 1-Octene | Octyl-1,3,5-trioxane, 20,[c] 19[d] |
| 1-Decene | Decyl-1,3,5-trioxane, 21,[c] 21,[d] 20[c] |
| 1-Dodecene | Dodecyl-1,3,5-trioxane, 24[c] |
| Methyl 4-pentenoate | Methyl 5-(1,3,5-trioxanyl)pentanoate, 10[c] |
| Methyl 10-undecylenate | Methyl 11-(1,3,5-trioxanyl)undecanoate, 19,[c] 15[d] |
| *Diethyl maleate* | Diethyl (1,3,5-trioxanyl)succinate, 27,[c] 84[c] |

[a] The mole ratio of 1,3,5-trioxan–olefin was 20:1 for terminal olefins and 70:1 for diethyl maleate. [b] Yields are based on the olefins employed. The consumptions were nearly quantitative in most cases. [c] Hanovia 450-w high-pressure mercury vapor lamps fitted into Pyrex tubes were used as the radiation source for these reactions. Temperature of reaction *ca.* 65°. [d] In sunlight. Initiated by acetophenone. [Reprinted from I. Rosenthal and D. Elad, *J. Org. Chem.*, **33**, 805 (1968). Copyright 1968 by The American Chemical Society. Reprinted by permission of the copyright owner.]



(104)

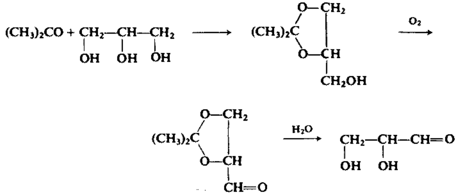
$R = H,$

$R' = C_5H_{11}, C_6H_{13}, C_8H_{17}, C_{10}H_{21}, CH_3COO(CH_2)_2, CH_3COO(CH_2)_8$

$R = R' = C_2H_5O\overset{\text{O}}{\overset{\|}{\text{C}}}-$

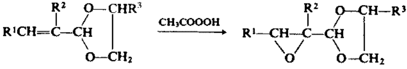
## 4. OXIDATION REACTIONS

The oxidation of hydroxymethyl groups of acetals is illustrated in the preparation of glyceraldehyde as shown in Eq. (105) [131].



(105)

Unsaturated cyclic acetals are oxidized with peracetic acid to epoxides Eq. (106) [132] (see Table XXX). The presence of sulfuric acid gives mainly unsaturated esters. The same oxidation on straight-chain acetals affords unsaturated esters (Eq. 107) [132].



(106)

$$CH_3-CH=CH-CH(OC_4H_9)_2 \xrightarrow{CH_3COOH} CH_3CH=CH-COOC_4H_9 \qquad (107)$$

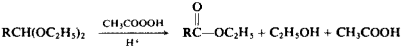
The latter reaction (Eq. 107) also takes place with saturated acetals and gives the esters in good yield (Eq. 108) [133]. A related reaction has been reported wherein an oxidation of metals affords the corresponding acid in some cases [134]. In other reports cyclic acetals are oxidized to peroxides Eq. (109) [135].

TABLE XXX

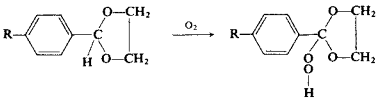
PERACETIC ACID OXIDATION OF 2-ALKENYL-1,3-DIOXOLANES TO 2-(EPOXYALKYL)-1,3-DIOXOLANES (SEE EQ. 93)[a]

| 2-Alkenyl-1,3-dioxolane, 1 mole | Peracetic acid (moles) | | Yield (%) | B.p., °C (mm Hg) | $n_D$ (30°C) |
|---|---|---|---|---|---|
| 2-(1-Propenyl) | 1.1 | *Solvent:* 2.65 gm of ethylacetate | 28 | 70–73 | 1.4337 |
| 2-(1-Propenyl)-4-methyl | 1.0 | *Reaction conditions:* 40°C, 4 hr | 46 | 81–83 (15) | 1.4291 |
| 2-Isopropenyl | 1.1 | | 64 | 78 (20) (9) | 1.4344 |
| 2-(1-Ethyl-1-pentenyl) | 1.1 | | 67 | 90–93 (5) | 1.4426 |
| 2-(1-Ethyl-1-pentenyl)-4-methyl | 1.1 | | 66 | 47–60 (0.4) | 1.4382 |
| 2-(β-Styryl)-4-methyl | 1.1 | | 45 | 111–112 (1) | 1.5197 |

[a] Data taken from D. L. Heywood and B. Phillips, *J. Org. Chem.* **25**, 1699 (1960).

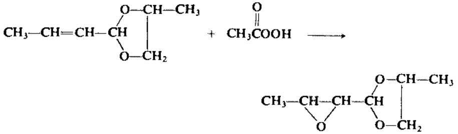


$$RCH(OC_2H_5)_2 \xrightarrow[H^+]{CH_3COOOH} R\overset{O}{\overset{\|}{C}}{-}OC_2H_5 + C_2H_5OH + CH_3COOH \qquad (108)$$



(109)

### 4-1. *The Preparation of 2-(1,3-Epoxypropyl)-4-methyl-1,3-dioxolane* [133]

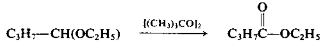


(110)

**CAUTION:** Use peracetic acid behind a shield. It is advisable to first run the reaction on 0.1 *M* scale or less.

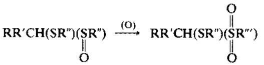
To a flask containing 12.8 gm (0.1 mole) of 2-(1-propenyl)-4-methyl-1,3-dioxolane is dropwise added with vigorous stirring 34.9 gm of a 24% solution (0.11 mole) of peracetic acid in ethyl acetate [136] while keeping the temperature at 40°C (about 1 hr). After an additional 7 hr at 40°C, the reaction mixture is cooled, 25 ml of ethylbenzene is added, and then the mixture fractionated to remove the acetic acid, ethylbenzene, and ethyl acetate. The residue is distilled under reduced pressure to afford 6.7 gm (46%), b.p. 81°–83°C (15 mm Hg), $n_D^{30}$ 1.4291.

Saturated acetals react with di-*t*-butyl peroxide to afford esters as shown in Eq. (111) [137–139]



$$C_3H_7{-}CH(OC_2H_5) \xrightarrow{[(CH_3)_3CO]_2} C_3H_7\overset{O}{\overset{\|}{C}}{-}OC_2H_5 \qquad (111)$$

The oxidation of dithioacetals by means of peroxide anion yields *S,S*-dioxides [139b].



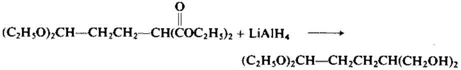
$$RR'CH(SR'')(\underset{O}{\underset{\|}{S}}R'') \xrightarrow{(O)} RR'CH(SR'')(\overset{O}{\overset{\|}{\underset{\underset{O}{\|}}{S}}}R''') \qquad (112)$$

More drastic oxidation of dithioacetals with *m*-chloroperbenzoic acid regenerates the carbonyl compound [139c].

## 5. REDUCTION REACTIONS

The acetal functional group does not appear to be affected by lithium aluminum hydride since side chain carboxyl groups are easily reduced to hydroxymethyl groups [140]. However, the presence of hydrogen chloride [141] or aluminum chloride [142] caused the reduction of the acetal to the ether function [141].

### *5-1. Preparation of 5-Hydroxy-4-hydroxymethylpentanal Diethyl Acetal [140]*



$$(C_2H_5O)_2CH{-}CH_2CH_2{-}CH(\overset{O}{\overset{\|}{C}}OC_2H_5)_2 + LiAlH_4 \longrightarrow (C_2H_5O)_2CH{-}CH_2CH_2CH(CH_2OH)_2 \qquad (113)$$

To a flask containing a solution of 14.6 gm (0.385 mole) of lithium aluminum hydride in 300 ml of absolute ether is added dropwise over a $2\frac{1}{2}$-hr period 83.3 gm (0.286 mole) of 3,3-diethoxy-1-propylmalonic acid diethyl ester. The excess hydride is cautiously decomposed by the dropwise addition of water, the ether separated, dried, concentrated, and the residue distilled under reduced pressure to afford 19.5 gm (33%), b.p. 140°–144°C (1.2 mm Hg), $n_D^{20}$ 1.4540, $d_4^{20}$ 1.10178.

The hydrogenolysis of ketals does not yield ketal derivatives in the presence of acid and rhodium or palladium, but gives ethers and alcohols as shown in Eq. (114) [143].

$$R'_2C(OR)_2 + H_2 \xrightarrow[Rh]{H^+} R'_2CHOR + ROH \qquad (114)$$

## 6. MISCELLANEOUS METHODS

(1) Synthesis of acetals of chloro- and bromoacetaldehyde by halogenation of vinyl acetate and subsequent reaction with alcohols [144–146].

(2) Preparation of bromo acetals by the HBr addition to acrolein while it is reacting with glycols to give β-bromo acetals [147].

(3) Preparation of bromo acetals by the bromination of paraldehyde and subsequent reaction with glycols [148].

(4) Preparation of spiro polymers containing five- to eight-membered cyclic ketal rings. For example, the reaction of pentaerythritol with cyclic diketones [149].

(5) Preparation of poly(vinyl butyral) [150].

(6) Preparation of polyvinyl acetals [151].

(7) Synthesis of allenic acetals via unsaturated carbenes generated from 5,5-dimethyl-*N*-nitrosooxazolidone [152].

(8) Preparation of β-keto acetals by the reaction of β-chlorovinyl ketones in the presence of methanolic sodium methoxide [153].

(9) Ketene acetals by the pyrolysis of ortho esters [154a–c].

(10) Preparation of α-hydroxy ketals from α-halo ketones [155a,b].

(11) Preparation of propargyl aldehyde acetals, $(RO)_2HC{\equiv}CH$, by the reaction of ground state $C_3$ with alcohols [156].

(12) Reaction of hexafluoroacetone with 2-substituted 1,3-dioxolanes affords ester fluoro acetals [157].

(13) Preparation of acetal choline phosphatides [158].

(14) Reaction of carbonyl compounds with epoxides [159a–c].

(15) Reaction of dialkyl sulfites with aldehydes to afford acetals in good yield [160].

(16) Acetals via dialkoxymethyl and dialkoxyethyl chlorocarbene intermediates [161a,b].

(17) Reaction of methyl vinyl ether with trimethyl orthoformate to yield 1,1,3,3-tetramethoxypropane [162a–c].

(18) Reaction of butyl vinyl ether with the dibutyl acetal of acetaldehyde [163a,b, 164].

(19) Preparation of a spiroacetal polymer from the diacetal of chloroacetaldehyde and pentaerythritol with sodium sulfide in DMSO [165].

(20) Reaction of triethyl orthoformate with diphenylketene [166].

(21) Preparation of dimethylketene dimethyl acetal by the reaction of the Grignard reagent of mesityl bromide and methyl orthoisobutyrate [167].

(22) Reaction of linear and cyclic ortho esters or orthoformates with peroxides to give peroxyacetals (or peroxy ortho esters) [168].

(23) Preparation of thioacetals by the reaction of substituted thiophenoxides with α-chlorobenzyl methyl ether [169].

(24) High-pressure acetal synthesis [170].

(25) Preparation of 1,3-oxathiolanes [171].

(26) Preparation of poly(ester–acetals) from the glycerol acetal of methyl azelaaldehydate [172].

(27) Cyclic ketals in the Robinson annelation of 1,3-cyclohexane-1,3-dione [173].

(28) Reaction of bromine with 2-ethoxy-5,6-dihydro-2*H*-pyran to produce a mixture of two geometrical isomers of 2-ethoxy-3,4-dibromotetrahydropyran [174].

(29) Improved procedure for the preparation of α-bromoaldehyde diethyl acetals [175].

(30) Preparation of 1,3-benzodioxanes [176a–c].

(31) Reaction of glyoxal with alcohols to give dioxanes or dioxolanes [177].

(32) Conversion of allyl ethers to acetals [178].

(33) Trimerization of aldehydes to trioxanes (cyclic acetal-like compounds) [179].

(34) Reaction of $CS_2$ with dialkyl malonates and then with dibromoalkanes to give cyclic mercaptals [180].

(35) Reaction of acetylene with organic disulfides to give rearranged dithioacetals such as $CH_3CH(SR)_2$[181].

(36) Synthesis of 1,1-diaryl-2,2-dimethoxyethanes from β-nitrostyrenes [182].

(37) The related 1,3-dioxolanation of α,β-unsaturated aldehydes with 1,2-bis(trimethylsilyloxy)ethane in the presence of trimethylsilyl trifluoromethanesulfonate as catalyst has been reported [183].

(38) Reaction of 2-acetylpiperidine with potassium *t*-butoxide followed by $CS_2$ and then methyl iodide to give 3,3-bis(methylthio)-1-(2-pyridinyl)-2-propen 1-one [184].

(39) Conversion of dialkylacetals to O,S-acetals by reaction of acetals with mercaptans [185].

(40) Reaction of α-haloketones with 2,2-dimethyl-1,3-propanediol to give 1,3-dioxanes(ketals) [186].

(41) Conversion of 3-chloro-l-methoxypropene to O,S-acetals Example: 3-(phenylthio)-3-methoxypropene [187].

(42) Preparation of diarylketene acetals with regiospecificity [188].

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## 1. INTRODUCTION

The most convenient laboratory methods of preparing carboxylic acid anhydrides involve either the reaction of acyl chlorides with carboxylic acids or their sodium salts or the reaction of acetic anhydride with acids boiling higher than acetic acid. The thermal dehydration of carboxylic acids has its limitations since not all acids afford anhydrides. The use of ketene in the laboratory is inconvenient but it is valuable in giving mixed acetic–carboxylic anhydrides. Industrially, acetic anhydride is prepared by this method.

The Diels–Alder reaction is valuable in adding maleic anhydride type structures to conjugated aliphatic and aromatic dienes.

Many aliphatic and aromatic anhydrides, depending on their structures, undergo various condensation, substitution, addition, and oxidation or reduction reactions to give substituted anhydrides.

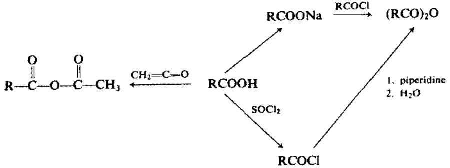
In addition to the mixed carboxylic anhydrides described above, this chapter will briefly describe some mixed sulfonic acid–carboxylic acid anhydrides.

Polymeric anhydrides can be prepared by the above techniques and are beginning to find various commercial uses. These are the styrene–maleic anhydride copolymers and the alkyl vinyl ether–maleic anhydride copolymers. The use of maleic acid or itaconic acid is widely used in the polymer field to give copolymers with anhydride functionality. A polymeric anhydride is described in this Chapter in Sections 2.A and 2.E.

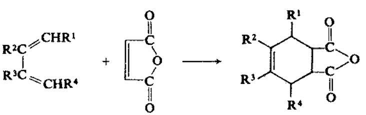
The anhydride functionality is very important in organic synthesis and can be reacted to form amides, esters, hydrazides and semicarbazides, etc.

## 2. CONDENSATION REACTIONS

The most important condensation methods involve (a) the reaction of carboxylic acids or derivatives with acyl halides or ketenes, (b) diacylation of water, and (c) the Diels–Alder reaction. These methods are shown in Eqs. (1) and (2).



(1)

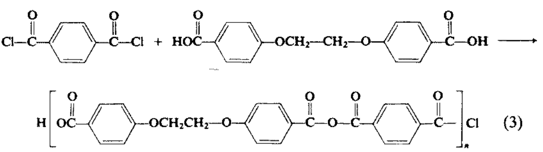


(2)

## A. Acylation of Carboxylic Acids by Acyl Halides

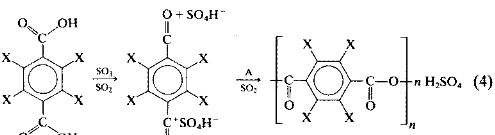
The reaction of acyl halides with carboxylic acids affords good yields of simple [1a–c] and mixed anhydrides [2]. The use of pyridine or triethylamine helps to remove the hydrogen chloride by-product. However, the preparation of benzoic anhydride from benzoic acid and benzoyl chloride has also been carried out in the absence of trialkylamines by heating under reduced pressure [3], in the presence of zinc chloride [4a] or by refluxing in chlorohydrocarbons such as methylene chloride [4b].

Polymeric anhydrides have been reported to be prepared by the reaction of terephthaloyl chloride with various aromatic dibasic acids containing ether or amide groups (Eq. 3) [5a].



(3)

M.p. 205°–209°C



(4)

Av. Mol. Wt. ~10,000

(A) (B)

Where X = Br or Cl

A report in the literature describes the preparation of diacylium cations from tetrahaloterephthalic acids and their reactivity with free tetrahaloterephthalic acids to produce homopolymers and heteropolymers with an anhydride backbone [5b]. The perhalo polyanhydrides are surprisingly stable to hydrolysis and are stable at relatively high temperatures.

### *2-1. Preparation of Heptanoic Anhydride* [1a]

$$C_6H_{13}COCl + C_5H_5N \longrightarrow [C_6H_{13}CO^+\ C_5H_5N]\,Cl^- \xrightarrow{C_6H_{13}COOH} (C_6H_{13}CO)_2O + C_5H_5\overset{+}{N}H\ \bar{Cl} \qquad (5)$$

To a flask containing 15.8 gm (0.2 mole) of dry pyridine and 25 ml of dry benzene is rapidly added with stirring 14.8 gm (0.1 mole) of heptanoyl chloride. The reaction is only slightly exothermic and then 13.0 gm (0.1 mole) of heptanoic acid is added dropwise (5 min) causing the temperature to rise to 60–65°C. After stirring for 10 min, the solid (pyridinium hydrochloride) is quickly filtered, washed twice with 25 ml portions of dry benzene, the benzene washings concentrated under reduced pressure, and the residue distilled to afford 19–20 gm (78–83%), b.p. 155–162°C (12 mm Hg), or 170–173°C (15 min).

Several other examples of this reaction are given in Table I.

### *2-2. Preparation of* p-*Nitrobenzoic-Benzylcarbonic Anhydride* [6]

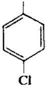
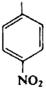
$$p\text{-}O_2N{-}C_6H_4COOH + C_6H_5CH_2OCOCl \xrightarrow{(C_2H_5)_3N} p\text{-}O_2N{-}C_6H_4COCOOCH_2C_6H_5 + (C_2H_5)_3\overset{+}{N}H\bar{Cl} \qquad (6)$$

To a flask equipped with a mechanical stirrer, dropping funnel, and condenser is added 3.4 gm (0.02 mole) of *p*-nitrobenzoic acid, 200 ml of ether, and 3.4 gm (0.02 mole) of benzyl chlorocarbonate. To the stirred mixture cooled to −78°C with a Dry Ice-acetone bath is added dropwise a solution of 2 gm (0.02 mole) of triethylamine in 10 ml of ether over a period of 1 hr. After 2 hr at −10°C the triethylamine hydrochloride is filtered to afford a 96% yield. The ether filtrate is successively washed with 0.5 *N* HCl, 2% $NaHCO_3$ solution, ice water, dried, concentrated under reduced pressure at 0°C to one half its volume, petroleum ether (b.p. 30–60°C) added to precipate 3.8 gm (63%) of the product, m.p. 64.5°–66°C (recryst. from chloroform and petroleum ether).

Recently it has been reported [7a–d] that triethylamine salts of carboxylic acids can be converted in one step to carboxylic anhydrides by reaction with phosgene or thionyl chloride at about 7°C (Eq. 6). The advantage of this method is that it avoids the need for often unavailable acid chlorides and difficult isolation procedures.

## TABLE I

### PREPARATION OF ANHYDRIDES BY THE REACTION OF ACYL HALIDES WITH CARBOXYLIC ACIDS

| RCOCl (moles) R = | R′COOH (moles) R′ = | Amine (moles) | Solvent (ml) | Reaction conditions Temp. (°C) | Time (hr) | Yield (%) | B.p., °C (mm Hg) or m.p., °C | Ref. |
|---|---|---|---|---|---|---|---|---|
| $C_6H_{13}$<br>(0.1) | $C_6H_{13}$<br>(0.1) | Pyridine<br>(0.2) | $C_6H_6$<br>(25) | 60–65 | 1/4 | 78–83 | 155–162 (12) | *a* |
| $C_6H_5$<br>(0.1) | <br>(0.1) | 0.2 | Ether<br>(100) | 25–30 | 1/4 | 69 | 66.5–70.0 | *b* |
| (0.1) | <br>(0.1) | 0.2 | $C_6H_6$<br>(100) | 25–30 | 1/4 | 65 | 130.0–130.5 | *b* |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **RCOOCl** | | | | | | | | |
| $C_2H_5$<br>(0.1) | $C_6H_5$<br>(0.1) | $(C_2H_5)_3N$<br>0.1 | Toluene<br>(150)<br>Ether<br>(50) | −5 to 0 | 1/2 | — | — | *c* |
| (0.2) | $O_2NC_6H_4$<br>(0.2) | 0.2 | Ether<br>(200) | −5 to 0 | 1/2 | — | 56–57 | *d* |
| (0.1) | H<br>(0.1) | 0.1 | Ether<br>(200) | −15 | 1/2 | — | — | *e* |
| $C_6H_5CH_2$<br>(0.02) | *p*-$O_2NC_6H_4$<br>(0.02) | 0.02 | Ether<br>(200 gm) | −78 to −10 | 1 | 63 | 64.5–66.0 | *f* |
| $(CH_3)_3C$<br>(0.065) | *p*-$O_2NC_6H_4$<br>(0.065) | 0.065 | Ether<br>(300) | −15 | 1 | 27 | 92–93 | *g* |

---

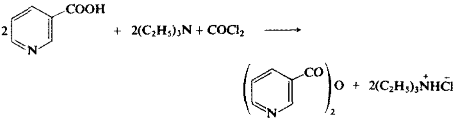
[a] C. F. H. Allen, C. J. Kibler, D. M. McLachlin, and C. V. Wilson, *Org. Syn. Coll.* **3**, 28 (1955). [b] J. M. Zeavin and A. M. Fisher, *J. Amer. Chem. Soc.* **54**, 3738 (1932). [c] J. A. Price and D. S. Tarbell, *Org. Syn. Coll.* **3**, 285 (1963); N. A. Leister and D. S. Tarbell, *J. Org. Chem.* **23**, 1152 (1958). [d] N. A. Leister and D. S. Tarbell, *J. Org. Chem.* **23**, 1149 (1958). [e] T. Parasaran and D. S. Tarbell, *J. Org. Chem.* **29**, 3422 (1964). [f] R. C. L. Chow and D. S. Tarbell, *J. Org. Chem.* **32**, 2188 (1967). [g] C. J. Michejda and D. S. Tarbell, *J. Org. Chem.* **29**, 1168 (1964).

$$2RCOOH + COCl_2 + 2(C_2H_5)_3N \longrightarrow (RCO)_2O + CO_2 + 2(C_2H_5)_3\overset{+}{N}H\overset{-}{Cl} \tag{7}$$

If thionyl chloride [7d] is used, the by-product is sulfur dioxide.

An example of this method using phosgene is the preparation of nicotinic anhydride (2–3).

***2-3. Preparation of Nicotinic Anhydride*** **[7b]**



(8)

**CAUTION:** This reaction must be carried out in a hood and all precautions should be taken in the use of phosgene.

To a three-necked, 500 ml, round-bottomed flask equipped with a mechanical stirrer, pressure-equalized dropping funnel, distillation column and head, are added 10.0 gm (0.081 mole) of nicotinic acid and 275 ml of dry benzene. The mixture is heated and 75 ml of benzene is distilled in order to remove traces of moisture. The distillation column and head are removed and replaced by a thermometer and a calcium chloride drying tube. The reaction stirred mixture is cooled to 5°C in an ice bath, 8.65 gm (0.086 mole) of triethylamine is added all at once, and then 34 gm of a 12.5% solution of phosgene (0.043 mole) in benzene (available from Matheson, Coleman and Bell) is added slowly in order to keep the temperature below 7°C. The reaction mixture is stirred for $\frac{3}{4}$ hr at room temperature, heated to boiling, and filtered hot using suction. The precipitated triethylamine hydrochloride is washed with three 25 ml positions of warm benzene and the resulting triethylamine amounts to 10.8 gm (96%). The combined benzene layer and washings are concentrated to dryness under reduced pressure at low temperatures. The solid residue is warmed with 75 ml of dry benzene, filtered hot, the remaining solid washed with two 5 ml portions of cold benzene, and the benzene filtrate and washes allowed to stand at 20°C for 2–3 hr. The anhydride crystallizes out of the benzene and is filtered. The solid is washed with two 4 ml portions of cold dry benzene and dried under reduced pressure to afford 6.25 gm (68%), m.p. 122–125°C. an additional 2.4 gm (25%) of product, m.p. 122–123°C is obtained from the combined benzene filtrate and washes.

Some additional examples illustrating the utility of this method are given in Table II.

## TABLE II

PREPARATION OF ANHYDRIDES BY THE REACTION OF CARBOXYLIC ACIDS WITH PHOSGENE

| Acid[b] (moles) | TEA[a] (moles) | Phosgene feed | | | | Solvent | Soln. by wt. of acid (%) | Yield of anhydride (%) |
|---|---|---|---|---|---|---|---|---|
| | | Form | Feed rate (moles/hr) | Moles | Temp. (°C) | | | |
| Acrylic<br>(2.0) | 2.0 | Liq. | 1.5 | 1.0 | −6 to 0 | Acetone | 35 | 73 |
| (1.95) | 2.0 | Gas | 2.0 | 1.0 | 5–18 | Ether | 25 | 50 |
| (1.95) | 2.0 | Gas | 0.82 | 0.82 | −5–0 | Ether | 10 | 66 |
| Methacrylic<br>(2.0) | 2.0 | Gas | 1.0 | 1.0 | 0–10 | Benzene | 11 | 90 |
| | | Thionyl chloride feed | | | | | | |
| Acrylic<br>(1.95) | 2.0 | Liq. | 1.2 | 1.0 | 0–5 | Benzene | 10 | 60 |

[a] Triethylamine. [b] Containing 0.1 % hydroquinone polymerization inhibitor. [Reprinted from T. K. Brotherton, J. Smith, Jr., and J. W. Lynn, *J. Org. Chem.* **26**, 1283 (1961). Copyright 1961 by the American Chemical Society. Reprinted by permission of the copyright owner.]

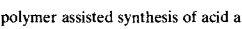
TABLE III

4-VINYLPYRIDINE COPOLYMER[a] FOR USE IN CONVERTING CARBOXYLIC ACIDS AND CARBOXYLIC ACID CHLORIDES TO ANHYDRIDES (7e)

| $R\overset{\overset{O}{\|}}{C}Cl$ R= | $R'\overset{\overset{O}{\|}}{C}OH$ R'= | Temp. (°C) | Time (min) | % Yield | Mass spectral data composition (mole %) $R\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}R'$ | $(R'CO)_2O$ | $(RCO)_2O$ |
|---|---|---|---|---|---|---|---|
| $C_6H_5$ | $CH_3$ | 0 | 60 | 86.4 | 0.74 | 0.12 | 0.14 |
| $CH_3$ | $C_6H_5$ | 0 | 15 | 84.9 | 0.75 | 0.09 | 0.16 |
| $C_6H_5$ | $(CH_3)_3C$ | 0 | 10 | 82.6 | 0.69 | 0.12 | 0.19 |
| $C_6H_5$ | $CH_2{=}CH{-}$ | 0 | 90 | 84.5 | 0.96 | 0 | 0.04 |
| $C_6H_5$ | $4NO_2C_6H_4$ | 25 | 120 | 97.6 | 0.95 | 0 | 0.05 |
| $2\text{-}CH_3C_6H_4$ | $2\text{-}CH_3C_6H_4$ | 25 | 360 | 90.8 | 1.00 | — | — |
| $4\text{-}CH_3C_6H_4$ | $4\text{-}CH_3C_6H_4$ | 25 | 180 | 93.2 | 1.00 | — | — |

[a] p4-VP-Reillex 425, Reilly Tar & Chem. Copolymer prepared from 4-Vinylpyridine copolymerized and crosslinked with 25% 4:1 divinylbenzene/4-ethyl styrene and contains 0.007 eq. pyridine/g.

Recently, a new polymer assisted synthesis of acid anhydrides has been reported [7e]. This method involves using a solid-phase copolymer of 4-vinyl pyridine in which a mixture of carboxylic acid and acid chloride in methylene chloride is passed over to give the acid anhydride in good yield. The process can be adapted for either batch or continuous processing provided the column is regenerated periodically.



$$RCOCl + R'COOH \xrightarrow[CH_2Cl_2 \atop -HCl]{\text{polymer}} R\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}R' \qquad (9)$$

Typical examples are described in Table III.

The reaction can also be carried in which the acid chloride is prepared in situ using thionyl chloride [7f].

$$2RCOOH + SOCl_2 \xrightarrow[CH_2Cl_2]{\text{polymer}} (RCO)_2O + 2HCl + SO_2 \qquad (9a)$$

Some typical examples are described in Table IV.

## B. Diacylation of Water

A related procedure involves the diacylation of water by the pyridinium salts of acyl halides to afford anhydrides (Eq. 10) [8]. The reaction was earlier described by Minunni [9] to involve an acyl pyridinium complex.

TABLE IV

4-VINYLPYRIDINE COPOLYMERS (SEE TABLE III) FOR USE IN CONVERSION OF ACIDS TO ACID ANHYDRIDES USING THIONYL CHLORIDE AT 22–25°C (AMBIENT)—BATCH MADE [7f]

| RCOOH<br>\|<br>R<br>0.005 mole | $SOCl_2$<br>0.55 equiv. | Copolymer<br>3.5–4.0<br>equiv. | Conditions<br>time<br>(min) | Yield of<br>anhydride<br>% |
|---|---|---|---|---|
| $CH_3$ | ✓ | ✓ | 5 | 88.8 |
| $CH_2{=}CH$ | ✓ | ✓ | 1–20 | 55.6 |
| $C_6H_5$ | ✓ | ✓ | 60 | 98.6 |
| 4-$CH_3$—$C_6H_4$ | ✓ | ✓ | 60 | 100 |

$$2RCOCl + 2C_5H_5N \longrightarrow 2[RCOCl\text{—}C_5H_5N] \xrightarrow{H_2O} (RCO)_2O + 2C_2H_5\overset{+}{N}H\overset{-}{Cl} \quad (10)$$

This reaction gives better yields when the complex is first prepared in the absence of water and then subsequently reacted with one-half mole of water per mole of acyl halide. Pyridine is preferred over the more basic triethylamine because the latter tends to effect dehydrohalogenation of aliphatic acyl halides to ketenes [10]. Some typical examples of this method are summarized in Table V and also given in Preparations 2-4 and 2-5. The reaction of ketenes with carboxylic acids to afford anhydrides is discussed in Section 2.D.

The benzoyl chloride–pyridine complex also reacts with hydrogen sulfide at about −20°C to afford an 85% yield of dibenzoyl sulfide (Eq. 11) [8].

$$2\,[RCOCl\text{—}C_5H_5N] + H_2S \longrightarrow (RCO)_2S + 2C_5H_5\overset{+}{N}H\overset{-}{Cl} \quad (11)$$

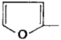
## *2-4. Preparation of Benzoic Anhydride* [11]

$$\begin{tikzcd} 2C_6H_5COCl + 2C_5H_5N \arrow[r] & 2[C_6H_5COC_5H_5N]^+\,Cl^- \arrow[d, "H_2O"] \\ & (C_6H_5CO)_2O + 2C_5H_5\overset{+}{N}H\overset{-}{Cl} \end{tikzcd} \quad (12)$$

To a flask containing 14.0 gm (0.1 mole) of benzoyl chloride and equipped with a stirrer is added 40 ml of dry dioxane and it is cooled to 5°C.

## TABLE V

### Preparation of Anhydrides by the Diacyclation of Water

| RCOCl (moles) R = | Pyridine (moles) | $H_2O$ (moles) | Solvent (ml) | Reaction Conditions Temp. (°C) | Reaction Conditions Time (hr) | Yield (%) | B.p., °C (mm Hg) or m.p., °C | Ref. |
|---|---|---|---|---|---|---|---|---|
| <br>(0.05) | 0.07 | 0.056 | Pet. ether<br>(60) | −20 | 1/12 | 64 | 71–73 | *a* |
| $C_6H_5$<br>(1.0) | 1.5 | 0.5 | Dioxane<br>(400) | 5–10 | 1/3 | 85–99 | 42 | *a* |
| $C_4H_9\overset{\overset{\displaystyle C_2H_5}{\vert}}{C}H$<br>(0.2) | 0.25 | 0.11 | $C_6H_6$<br>(150) | 5–10 | 1/2 | 42.0–43.5 | 149–152 (8) | *a* |
| *p*-Cl—$C_6H_4$<br>(0.1) | 0.6 | 5.6 | — | 80–100 | 1/12 | 96–98 | 192–193 | *b* |
| *o*-Cl—$C_6H_4$<br>(0.1) | 0.1 | 0.11 | Dioxane<br>(40) | 5–10 | 1/2 | 50.0 | 77–79 | *a* |
| *p*-I—$C_6H_4$<br>(0.05) | 0.05 | 0.056 | Dioxane<br>(20) | 5–10 | 1/2 | 46.0 | 227–229 | *a* |
| $CH_3$<br>(0.50) | 0.25 | 0.11 | $C_6H_6$<br>(150) | 5–10 | 1/2 | 20–24 | 136–139 (760) | *a* |
| $C_2H_5$<br>(0.40) | 0.25 | 0.11 | $C_6H_6$<br>(150) | 5–10 | 1/2 | 29.0–31.0 | 163–166 (760) | *a* |

[a] H. Adkins and Q. E. Thompson, *J. Amer. Chem. Soc.* **71**, 2242 (1949).

[b] C. F. H. Allen, C. J. Kibler, D. M. McLachlin, and C. V. Wilson, *Org. Syn. Coll.* **3**, 28 (1955).

Then 10 ml (0.1 mole) of dry pyridine is rapidly added at 5–10°C followed by 1.0 ml (0.056 mole) of water. After stirring for 10–15 min at 0–5°C, the reaction mixture is then poured into a mixture of 75 ml of conc. hydrochloric acid, 75 gm of cracked ice, and 350 ml of water. The product is filtered, washed first for 1 min with a cold 5% solution of sodium bicarbonate and then with water. The product is dried to afford 11.0 gm (97%), m.p. 43°C (recrystallized from a mixture of ether–petroleum ether).

### *2-5. Preparation of* p-*Chlorobenzoic Anhydride* [12]

$$2p\text{-Cl—C}_6H_4COCl + 2C_5H_5N \longrightarrow 2[p\text{-Cl—C}_6H_4COC_5H_5N]^+\,Cl^- \xrightarrow{H_2O}$$

$$(p\text{-Cl—C}_6H_4CO)_2O + 2C_5H_5\overset{+}{N}H\overset{-}{Cl} \qquad (13)$$

To a flask containing 17.5 gm (0.1 mole) of *p*-chlorobenzoyl chloride is added 50 ml (0.6 mole) of pyridine and the mixture heated for 5 min on the steam bath. The mixture is poured upon 100 gm of cracked ice and 50 ml of concentrated hydrochloric acid, allowed to warm to room temperature, filtered, the solid washed successively with 15 ml of methanol and 15 ml of dry benzene, and dried to afford 14.2–14.6 gm (96–98%), m.p. 192–193°C (recrystallized from 250 ml of dry benzene).

## C. Reaction of Acyl Halides with Salts of Carboxylic Acids

The general reaction of acyl halides with carboxylic acid salts may be written as in Eq. (14).

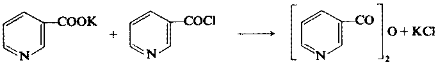
$$RCOOM + R'COCl \longrightarrow RCOOCOR' + MCl \qquad (14)$$

where M = alkali metal or Tl; R may or may not be equal to R′; and R′ = alkyl, aryl, or H (for one of the substituents).

The reaction of the acid chlorides of carboxylic acids with sodium [13a,b] or silver [14a–c] carboxylates gives good yields of anhydrides. The reaction can be applied to the preparation of mixed aliphatic anhydrides [14b, 15], but is more difficult to apply to the mixed aromatic anhydrides [16a].

A patent describes the use of phase-transfer catalyst to react acid chlorides in a water-immiscible solvent with an aq. solution of RCOOM (M = Na or K) to give high yields of anhydride in good purity [16b].

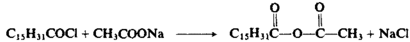
### *2-6. Preparation of Nicotinic Anhydride* [13a]



(15)

To a 500 ml three-necked, round-bottomed flask equipped with a mechanical stirrer, dropping funnel, and condenser fitted with a drying tube is added 40.6 gm (0.33 mole) of nicotinic acid and 100 ml of dry nitrobenzene. (NOTE: The use of other solvents gives lower yields of product: *p*-cymene, 26.6%; *o*-dichlorobenzene, 78.3%.) Thionyl chloride [39.3 gm (0.33 mole)] is added dropwise over a 10 min period and then the temperature is raised to 210°C. The reaction is kept at 210°C for 1 hr or until all the gas evolution has ceased. The reaction mixture is cooled, 53.1 gm (0.33 mole) of potassium nicotinate is added in one portion and the reaction mixture again heated to 210°C. After 3 hr the reaction mixture is cooled to 100°C and transferred to a $1\frac{1}{2}$-liter beaker containing 1 liter of benzene and 10 gm of decolorizing charcoal. The benzene solution is boiled for 10 min, filtered hot, cooled, and the resulting crystalline product filtered to afford a total of 66.6 gm (88.9%), m.p. 122.5–123.5°C (recrystallized from benzene).

### *2-7. Preparation of Acetic–Palmitic Anhydride* [15]



$$C_{15}H_{31}COCl + CH_3COONa \longrightarrow C_{15}H_{31}\overset{O}{\overset{\|}{C}}{-}O{-}\overset{O}{\overset{\|}{C}}{-}CH_3 + NaCl \qquad (16)$$

To a flask containing 27.4 gm (0.1 mole) of palmitoyl chloride is added 8.5 gm (0.103 mole) of sodium acetate over a 5-min period. The mixture is heated in an oil bath at 80–100°C for $\frac{1}{2}$ hr, cooled, and petroleum ether (b.p. 65–67°C) added to extract the product. Concentration of the petroleum ether affords 20.9 gm (70%), m.p. 62.5°C.

Smalley and Suschitzky [17] reported that mixed aromatic anhydrides as well as some aliphatic anhydrides have been made in high yield and purity by shaking an aqueous solution of the alkali metal carboxylate with an acyl halide at room temperature in the presence of a tertiary amine catalyst. This procedure affords benzoic anhydride in 97.5% yield, whereas the more involved procedure of reacting benzoic acid with acetic anhydride affords only 72–74% [18].

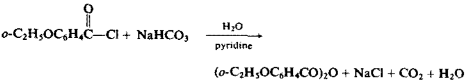
### *2-8. Preparation of Benzoic Anhydride* [17]

$$C_6H_5COONa + C_6H_5COCl \xrightarrow[\text{pyridine}]{H_2O} (C_6H_5CO)_2O + NaCl \qquad (17)$$

To a beaker containing 150 ml of an aqueous solution of 14.4 gm (0.1 mole) of sodium benzoate and two drops of pyridine is added slowly with stirring 14.0 gm (0.1 mole) of benzoyl chloride. The resulting solid is filtered, washed with water then petroleum ether, and dried to afford 22.1 gm (97.5%), m.p. 40–41°C.

An improvement of Preparation 2-8 involves the direct reaction of aromatic acid chlorides with aqueous sodium bicarbonate containing some pyridine to give anhydrides in high yields [19]. Substitution of the sodium bicarbonate with water-insoluble bases or alkali hydroxides leads to lower yields [20].

### *2-9. Preparation of* o-*Ethoxybenzoic Anhydride* [19]



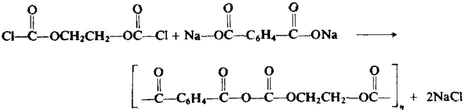
$$o\text{-}C_2H_5OC_6H_4\overset{O}{\overset{\|}{C}}\text{—}Cl + NaHCO_3 \xrightarrow[\text{pyridine}]{H_2O} (o\text{-}C_2H_5OC_6H_4CO)_2O + NaCl + CO_2 + H_2O \qquad (18)$$

To a flask containing 16.8 gm (0.2 mole) of sodium bicarbonate dissolved in 300 ml of water and 4 ml of pyridine is added dropwise 36.9 gm (0.2 mole) of *o*-ethoxybenzoyl chloride at 20°C over a $\frac{1}{2}$-hr period. The reaction mixture is filtered and dried to afford 29.1 gm (92.7%), m.p. 77.5°C (recrystallized from benzene–ethanol).

Mixed aliphatic–aromatic anhydrides can be made by the reaction of acyl halides and sodium carboxylates and is illustrated by the preparation of formic-benzoic anhydride [21 described in Table VI. Mixed anhydrides readily undergo disproportionation above room temperature and thus always contain some symmetrical anhydride impurities [22].

Recently Taylor [23] and co-workers have also reported that thallium(I) carboxylates react with thionyl chloride in ether at room temperature or below to afford symmetrical anhydrides in 96–98% yields. Whether this reaction can be applied to sodium or other alkali metal carboxylates is yet to be determined. However, earlier it had been reported that potassium nicotinate reacts with thionyl chloride to give nicotinanhydride in lower yields than from the corresponding acyl halide [13a,b].

Polymeric anhydrides can be prepared by the reaction of diacyl halides and disodium carboxylates. A typical example is the reaction of ethylene glycol bis(chloroformate) with disodium *p*-terephthalate in DMF and triethylamine at 155°C for 3 hr [24]. The product is added to ice water to give poly(terephthalic ethylene carbonic anhydride), m.p. 155–160°C (Eq. 19) [24].

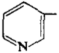
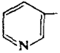
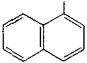


$$Cl\text{—}\overset{O}{\overset{\|}{C}}\text{—}OCH_2CH_2\text{—}O\overset{O}{\overset{\|}{C}}\text{—}Cl + Na\text{—}O\overset{O}{\overset{\|}{C}}\text{—}C_6H_4\text{—}\overset{O}{\overset{\|}{C}}\text{—}ONa \longrightarrow \left[\text{—}\overset{O}{\overset{\|}{C}}\text{—}C_6H_4\text{—}\overset{O}{\overset{\|}{C}}\text{—}O\text{—}\overset{O}{\overset{\|}{C}}\text{—}OCH_2CH_2\text{—}O\overset{O}{\overset{\|}{C}}\text{—}\right]_n + 2NaCl \qquad (19)$$

## TABLE VI

### PREPARATION OF ANHYDRIDES BY THE REACTION OF ACYL HALIDES WITH SALTS OF CARBOXYLIC ACIDS

| RCOOM (1.0 mole) R = | M | R′COCl (1.0 mole) R′ = | Catalyst (gm) | Solvent (ml) | Reaction conditions Temp. (°C) | Reaction conditions Time (hr) | Yield (%) | B.p., °C (mm Hg) or m.p., °C | $n_D$ (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|
| $C_2H_5$ | Ag | $C_2H_5$ | — | — | — | — | 88 | 165 (760) | 1.4041 (17) | *a* |
| $C_3H_7$ | Ag | $C_3H_7$ | — | — | — | — | — | 193 (760) | 1.4143 (18) | *a* |
| $C_{15}H_{31}$ | Ag | $C_{15}H_{31}$ | — | — | — | — | — | 62.6 | 1.4359 (70) | *a* |
| $C_{17}H_{35}$ | Ag | $C_{17}H_{35}$ | — | — | — | — | — | 70.5 | 1.4362 (80) | *a* |
| H | Na | $CH_3$ (1.18) | — | Ether (67) | 23–27 | 6 | 64 | 27–28 (10)<br>38–38.5 (39) | 1.3880 (20) | *b* |
| *i*-$C_3H_7$ | Na | *i*-$C_3H_7$ | — | — | — | — | 67 | 92 (34) | — | *c* |
| *t*-Bu | Na | *t*-Bu | — | — | — | — | 78 | 5 (28) | — | *c* |
| $CH_3$ | Na | $C_{15}H_{31}$ | — | — | 60–70 | 1/2 | 70 | 62.5 | — | *d* |
| H | Na | $C_6H_5$ | — | Diethylene glycol dimethyl ether (100) | 9–15 | 3.7 | 11 | 64.5–69.0 (0.45–0.60) | — | *e* |

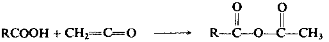
| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
|  | K |  | — | $C_6H_5NO_2$ (100) | 210 | 3 | 89 | 122.5–123.5 | — | *f* |
| | | *o*-$C_2H_5O—C_6H_4$ | $NaHCO_3$ (16.8) | $H_2O$ (300), pyridine (4) | 20 | 1/2 | 93 | 77.5 | — | *g* |
| | |  8 gm | $Na(CO_3)_2$ (4) | Pyridine (2.5), $H_2O$ (a few drops) | — | — | 80 | 145–146 | — | *h* |
| $C_6H_5$ | Tl | $CH_3$ | — | Ether | 5 | 1/4 | 95[k] | — | — | *i* |
| $C_6H_5$ | Tl | $C_6H_5$ | — | Ether | 35 | 4 | 100[k] | — | — | *i* |
| *t*-Bu | Tl | *t*-Bu | — | Ether | 25 | 1 | 100[k] | — | — | *i* |
| $C_6H_5$ | Na | $C_6H_5$ | Pyridine (20 drops/ mole) | $H_2O$ | 25 | 1 | 97.5 | 41 | — | *j* |
| *p*-Br—$C_6H_4$ | Na | $C_6H_5$ | Pyridine (20 drops/ mole) | $H_2O$ | 25 | 1 | 75 | 82 | — | *j* |

---

[a] G. S. Whitby, *J. Chem. Soc.* 1458 (1926). [b] L. I. Krimen, *Org. Syn.* **50**, 1 (1970). [c] J. B. Conn, G. B. Kistiakowsky, R. M. Roberts, and E. A. Smith, *J. Amer. Chem. Soc.* **64**, 1747 (1942). [d] A. W. Ralston and R. A. Reck, *J. Org. Chem.* **11**, 624 (1946). [e] G. F. Fanta, *J. Org. Chem.* **29**, 981 (1964). [f] C. O. Badgett, *J. Amer. Chem. Soc.* **69**, 2231 (1947). [g] P. Rambacher and S. Mäke, *Angew. Chem.* **80**, 487 (1968). [h] F. F. Blicke, *J. Amer. Chem. Soc.* **49**, 2843 (1927). [i] E. C. Taylor, G. W. McLay, and A. McKillop, *J. Amer. Chem. Soc.* **90**, 2422 (1968). [j] R. K. Smalley and H. Suschitzky, *J. Chem. Soc.* 755 (1964). [k] IR and NMR spectra reveal 1–3% of the corresponding symmetrical anhydride.

## D. Reaction of Carboxylic Acids with Ketene

Hurd and Dull [22] were the first to describe a general procedure for the preparation of unsymmetric acetic anhydrides from ketene and carboxylic acids (Eq. 18). These acetic carboxylic anhydrides were thermally unstable and could be converted into acetic acid and the symmetric anhydride by heating at atmospheric pressure (Eq. 19) [22, 25]. Some examples are given in Table VII. Most other mixed anhydrides can be distilled at low temperature under reduced pressure.



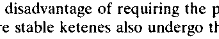
$$RCOOH + CH_2{=}C{=}O \longrightarrow R{-}\overset{O}{\overset{\|}{C}}{-}O{-}\overset{O}{\overset{\|}{C}}{-}CH_3 \qquad (20)$$

$$R{-}\overset{O}{\overset{\|}{C}}{-}O{-}\overset{O}{\overset{\|}{C}}CH_3 + RCOOH \longrightarrow (R\overset{O}{\overset{\|}{C}})_2O + CH_3COOH \qquad (21)$$

This method has the disadvantage of requiring the prior production of ketene [26]. Other more stable ketenes also undergo this reaction to give mixed anhydrides [27a,b].

TABLE VII

PREPARATION OF SYMMETRICAL ANHYDRIDES BY THE THERMAL DECOMPOSITION OF ACETIC CARBOXYLIC ANHYDRIDES



$$2R\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}CH_3 \rightarrow (RCO)_2O + (CH_3CO)_2O$$

| Mixed anhydride $CH_3COOCOR$ (mole) | Reaction conditions Temp. (°C) | Time (hr) | Yield $(RCO)_2O$ (%) | B.p., °C (mm Hg) or m.p., °C | Ref. |
|---|---|---|---|---|---|
| Acetic–caproic (0.5) (contains 0.5 mole of free caproic acid) | 220 | 3–4 | 80–87 | 109–112 (3) and 118–121 (6) | *a* |
| Acetic–mesitoic | 200 | 6 | — | 104 | *b* |
| Acetic–benzoic | 210 | — | 96 | 210–210.5<br>41.5 | *c* |

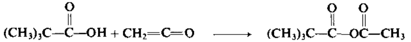
[a] J. W. Williams and J. A. Krynitsky, *Org. Syn. Coll.* **3**, 164 (1955). [b] C. A. Bunton and S. G. Perry, *J. Chem. Soc.* 3070 (1960). [c] C. D. Hurd and M. F. Hull, *J. Amer. Chem. Soc.* **54**, 3427 (1932).

### *2-10. Preparation of n-Caproic Anhydride* [25]

$$CH_3(CH_2)_4COOH + CH_2{=}C{=}O \longrightarrow [CH_3(CH_2)_4COOCOCH_3] \xrightarrow[\text{heat}]{CH_3(CH_2)_4COOH} [CH_3(CH_2)_4CO]_2O + CH_3COOH \quad (22)$$

To an ice-cooled flask containing 116 gm (1.0 mole) of *n*-caproic acid is added 21.0–23.10 gm (0.5–0.55 mole) of ketene at a rate of 0.45 mole/hr [28]. The reaction mixture is fractionally distilled at atmospheric pressure to afford a forecut of acetone, acetic acid, and acetic anhydride. The oil bath is raised to 220°C over a 1-hr period, kept there for 3 hr to ensure complete removal of acetic acid, and then cooled. The distillation is continued under reduced pressure to afford 86–95 gm (80–87%), b.p. 109–112°C (3 mm Hg) and b.p. 118–121°C (6 mm Hg).

### *2-11. Preparation of Acetic–Pivalic Anhydride* [29]



$$(CH_3)_3C{-}\overset{O}{\overset{\|}{C}}{-}OH + CH_2{=}C{=}O \longrightarrow (CH_3)_3C{-}\overset{O}{\overset{\|}{C}}{-}O\overset{O}{\overset{\|}{C}}{-}CH_3 \quad (23)$$

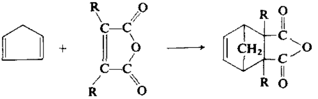
To an ice-cooled flask containing 35.0 gm (0.29 mole) of pivalic acid is added ketene as in Preparation (2-10) at 0–5°C to afford 21.8 gm (44.1%) of acetic pivalic anhydride; $n_D^{20}$ 1.4027; neutral equivalent 73.1 (calcd. 72.1) The product was not distilled since the mixed anhydrides thermally decompose to two symmetrical anhydrides (see Preparation 2-10).

Some other examples illustrating the method of Preparation 2-11 are shown in Table VIII.

Mixed acetic anhydrides can also be made by the reaction of acyl chloride with sodium acetate or by the reaction of the free acid with acetyl chloride in the presence of pyridine [30a–e].

## E. Diels–Alder Reaction

The Diels–Alder reaction has been reviewed earlier [31, 32]. The 1,4-addition of unsaturated anhydrides to conjugated aliphatic or aromatic dienes affords cyclic anhydrides. Useful anhydrides are maleic, citraconic (methylmaleic), pyrocinchonic (dimethylmaleic), itaconic anhydride, dibromomaleic, and acetoxymaleic. For example, all these anhydrides react with cyclopentadiene to give the appropriate adducts (Eq. 24) [31].



(24)

TABLE VIII

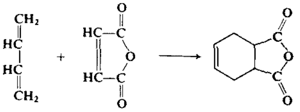
Reaction of Ketene[a] with Carboxylic Acids at 0°–5°C in the Absence of Solvents to Afford Mixed Acetic Anhydrides

| Carboxylic acid | Yield (%) | B.p., °C (mm Hg) or m.p., °C | $n_D^{20}$ (°C) | Ref. |
|---|---|---|---|---|
| Acetic | 100 | 136–138 (760) | — | *g* |
| Chloroacetic | 62 | 27–30 (0.01) | 1.4280 (25) | *h* |
| Chloroacetic | 71 | —[c] | 1.4301 (25) | *h* |
| Propionic | 54 | 39–40 (10) | 1.3969 | *h* |
| Butyric | 41 | 40–42 (5) | 1.4043 | *h* |
| Butyric | — | 147–160 (760)[d]<br>70–85 (18) | — | *g* |
| Isobutyric | 58 | 38.5–40.5 (7) | 1.3991 | *h* |
| α-Methylbutyric | 77 | —[c] | 1.4063 | *h* |
| β-Methylbutyric | 52 | —[c] | 1.4055 | *h* |
| Valeric | 51 | 56–59 (6) | 1.4092 | *h* |
| Pivalic | 44[b] | —[c] | 1.4027 | *i* |
| Caproic | 53 | —[c] | 1.4145 | *h* |
| Heptanoic | 62 | —[c] | 1.4186 | *h* |
| Octanoic | 48 | —[c] | 1.4233 | *h* |
| Benzoic[e] | 100 | —[c] | — | *g* |
| *p*-Nitrobenzoic | — | 75.5–77.0[f] | — | *j* |

[a] A slight excess of ketene was used. [b] Reaction carried out at first at the melting point of pivalic acid (35.5°C) and then at 0°–5°C. [c] The anhydride was not distilled. [d] Above this temperature decomposition to butyric anhydride occurs. [e] Reaction carried out in 100 ml of ether. [f] Recrystallized from petroleum ether. [g] C. D. Hurd and M. F. Dull, *J. Amer. Chem. Soc.* **54**, 3427 (1932). [h] W. R. Edwards, Jr., and E. C. Sibille, *J. Org. Chem.* **28**, 674 (1963). [i] W. R. Edwards, Jr., and R. J. Eckert, Jr., *J. Org. Chem.* **31**, 1283 (1966). [j] C. A. Bunton and S. G. Perry, *J. Chem. Soc.* 3070 (1960).

An example illustrating this method for linear olefins is given in Preparation 2-12 for the condensation of maleic anhydride with 1,3-butadiene to give $\Delta^4$-tetrahydrophthalic anhydride. Other examples of related condensations are shown in Table IX.

### *2.12. Preparation of Tetrahydrophthalic Anhydride* [33]



(25)

## TABLE IX

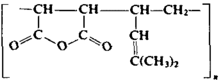
### REACTION OF DIENES WITH MALEIC ANHYDRIDE OR DERIVATIVES

| Diene (moles) | Olefinic anhydride (moles) | Reaction conditions Temp.[n] (°C) | Reaction conditions Time (hr) | Yield[o] (%) | M.p. (°C) | Ref. |
|---|---|---|---|---|---|---|
| 1,3-Butadiene (2.0) | Maleic[a]<br>2.0 | 50–75 | 3 | 96–97 | 99–102 | *b* |
| 2,3-Dimethyl-1,3-butadiene (1.0) | 1.0 | 0 | 12 | 96 | 67 | *c* |
| 1-*o*-Chlorophenyl-4-phenyl-1,3-butadiene | 1.0[d] | 80–100 | 1 | 48 | 178–179 | *e* |
| 2-Methyl-1-vinyl-1-cyclohexene (1.0) | 1.0[a] | 25 | 48 | — | 114.0–114.5 | *f* |
| Indene (1.0) | 0.71[a] | 250 | 5 | 22 | 187–188 | *g* |
| 1,3-Di-*p*-tolyisobenzofuran (1.0) | 1.1[a] | 25 | 1/12 | 92 | 256–258 | *h* |
| Anthracene (1.0) | Citraconic[i]<br>0.3 | 120 | 84 | 96 | — | *j* |
| Butadiene (1.0) | Dimethylmaleic[a]<br>0.5 | 190–205 | 72 | 21 | — | *k* |
| 2,3-Dimethyl-1,3-butadiene | 3,4-Dihydro-8,9-acephenanthrene-1,2-dicarboxylic anhydride[l] | 160–180 | 24 | 67–73 | 187.5–188.0 | *m* |

[a] $C_6H_6$ is the solvent. [b] A. C. Cope and E. C. Herrick, *J. Amer. Chem. Soc.* **72**, 984 (1950). [c] E. H. Farmer and F. L. Warren, *J. Chem. Soc.* 3221 (1931). [d] No solvent. [e] F. Bergmann, H. Weizman, and D. Shapiro, *J. Org. Chem.* **9**, 408 (1944). [f] J. W. Cook and C. A. Lawrence, *J. Chem. Soc.* 58 (1938). [g] K. Alder, F. Pascher, and H. Vogt, *Ber.* **75**, 1501 (1942). [h] R. Adams and R. W. Wearn, *J. Amer. Chem. Soc.* **62**, 1233 (1940). [i] Dry toluene is the solvent. [j] W. E. Bachmann and L. B. Scott, *J. Amer. Chem. Soc.* **70**, 1458 1462 (1948). [k] R. B. Woodward and R. B. Loftfield, *J. Amer. Chem. Soc.* **63**, 3167 (1941). [l] Dioxane is the solvent. [m] L. F. Fieser, M. Fieser, and E. B. Hershberg, *J. Amer. Chem. Soc.* **58**, 1463 (1936). [n] Reaction temperatures higher than the boiling point of the solvent indicate sealed tube reactions. [o] In most cases the lower yields are due to polymer formation.

A flask containing 500 ml of dry benzene and 196 gm (2 moles) of maleic anhydride is heated with a pan of hot water while butadiene is introduced rapidly (0.6–0.8 liter/min) from a commercial cylinder. The solution is stirred rapidly and the heating is stopped after 3–5 min when the temperature reaches 50°C. In 15–25 min the reaction causes the temperature of the solution to reach 70–75°C. The absorption of the rapid stream of butadiene is nearly complete in 30–40 min. The addition of butadiene is continued at a slower rate for a total of 2½ hr. The solution is poured into a 1-liter beaker which is covered and kept at 0–5°C overnight. The product is collected on a large Büchner funnel and washed with 250 ml of b.p. 35–60°C petroleum ether. A second crop is obtained by diluting the filtrate with an additional 250 ml of petroleum ether. Both crops are dried to constant weight in an oven at 70–80°C to yield 281.5–294.5 gm (96–97%, m.p. 99–102°C). Recrystallization from ligroin or ether raises the melting point to 103–104°C.

It should be noted that maleic anhydride reacts with many olefins (2-methyl-2,4-hexadiene [34a,b], 4-*n*-propyl-1,3-heptadiene [35], styrene [36], stilbene [36, 37], 2-methyl-1,3-pentadiene [38], 3-methyl-1,3-pentadiene [37]) to give mainly polymeric products. For example, the product of the condensation with 4-methyl-1,3-pentadiene has structure (I) [38–40]. Maleic anhydride also helps to initiate the polymerization of 2-methyl-*n*-1,3-pentadiene with vinyl acetate [38].

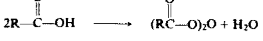


(I)

The use of pure maleic anhydride is recommended since some free maleic acid can cause isomerization [41] or initiate polymerization [42] of some diene systems.

## 3. ELIMINATION REACTIONS

The most important elimination reaction used for the preparation of anhydrides involves the dehydration of acids (Eq. 24) using either (a) thermal methods, (b) acetic anhydride, or (c) other more special dehydrating agents. The dealcoholation of diesters also affords anhydrides.



$$2R\overset{O}{\overset{\|}{C}}{-}OH \longrightarrow (R\overset{O}{\overset{\|}{C}}{-}O)_2O + H_2O \qquad (26)$$

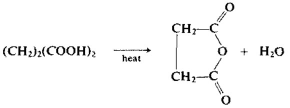
## A. Thermal Method

The thermal method gives poor yields in laboratory preparations of anhydrides from aliphatic [43] and aromatic carboxylic acids [44a,b]. This method also suffers from the disadvantage that cyclic anhydrides with rings larger than five or six members tend to give low yields or polymers.

For example:

$$(COOH)_2 \xrightarrow[\text{heat}]{} CO_2 + HCOOH \tag{27}$$

$$CH_2(COOH)_2 \xrightarrow[\text{heat}]{} CH_3COOH + CO_2 \tag{28}$$



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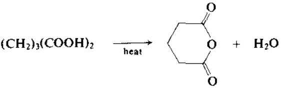

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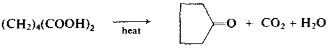

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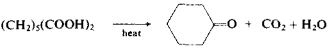
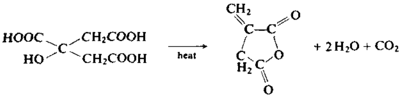


(32)

Cyclic anhydrides can be obtained by the distillation of some of the diacids at atmospheric or under reduced pressure conditions. For example, heating citric acid monohydrate at atmospheric pressure affords itaconic anhydride in 37–47% yield [45].

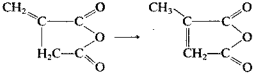
### *3-1. Preparation of Itaconic Anhydride* [45, 46a]



(33)

To a flask equipped with a 12 mm diameter ground glass adaptor tube bent for downward distillation and joined to a 100 cm condenser is added 200 gm (0.95 mole) of citric acid monohydrate. An ice-cooled flask and a cold trap are connected to the condenser. The flask containing the citric acid is heated rapidly with a wide flame of the Meker burner so that in 12–15 min the distillation at 175–190°C is complete. The distillation is stopped earlier if the vapors in the reaction flask become yellow. Superheating of the citric acid will cause rearrangement to citraconic anhydride. The water is quickly separated from the distillate and the itaconic anhydride layer dried to afford 40–50 gm (37–47%), m.p. 67–68°C. Long time contact of the water with the anhydride causes it to hydrolyze to itaconic acid, m.p. 162–165°C.

Itaconic anhydride isomerizes to citraconic anhydride either by distillation or by simple melting [46b].



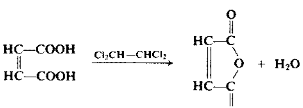
(34)

The use of certain amines (pyridine) acts as a catalyst for this isomerization [46b].

In another example, 1-carboxycyclohexane-1-acetic acid is distilled under reduced pressure to afford a 76% yield of the anhydride, m.p. 55°C [47].

A more convenient procedure involves the azeotropic removal of water by heating a diacid with tetrachloroethane. For example, maleic anhydride can be obtained in 90% yield by this method [48].

### *3-2. Preparation of Maleic Anhydride* [48]



(35)

To a flask equipped with a Dean–Stark trap, condenser, and mechanical stirrer is added 116 gm (1.0 mole) of maleic acid and 120 ml of tetrachloroethane. The contents are heated, the water (18 ml, 1.0 mole) distilled off as the azeotrope, and the residue distilled under reduced pressure to afford 87.7 gm (89.5%) of the anhydride, b.p. 82–84°C (15 mm), m.p. 53°C. The residue remaining in the flask consists of about 10 gm of fumaric acid, m.p. 287°C.

Fumaric and maleic acids both give maleic anhydride on heating. Fumaric acid must first be heated to a higher temperature to effect its conversion to maleic acid prior to its dehydration.

It has been reported that hexahydrobenzoic acid can be converted to the anhydride by heating at 640–666°C in a copper tube reactor at 8 mm Hg using an organophosphate catalyst (e.g. triethylphosphate) [48b].

## B. Acetic Anhydride Method

The reaction of di- and polycarboxylic acids with refluxing acetic anhydride affords good yields of anhydrides, as seen by the many examples shown in Table X. In many cases where the direct distillation of the carboxylic acids leads to impure products the use of acetic anhydride affords a purer anhydride product. A recent example is the preparation of 1,2,3,4-cyclopentane dianhydride, as seen in Table X. Attempts to prepare this anhydride by heating the dry 1,2,3,4-cyclopentanetetracarboxylic acid at 130–230°C/10 mm Hg for 1–2 hr afforded a mixture of mono- and dianhydride.

Furthermore, attempts to prepare cyclic anhydrides of the $\alpha$-alkyl glutaric acids by direct distillation under reduced pressure were unsuccessful but these can be obtained by using the acetic anhydride method (see Table X).

The use of an excess of acetic anhydride allows one to keep the reaction temperature at 136°C.

Recently polymeric anhydrides have been prepared using this method. For example, 1,3-bis(*p*-carboxyphenoxy)propane is refluxed with acetic anhydride to afford an 87% yield of poly[1,3-bis(*p*-carboxyphenoxy)-propane] anhydride, m.p. 102–103°C [49].

### *3.3. Preparation of Diphenylacetic Anhydride* [50]

$$2(C_6H_5)_2CHCOOH + (CH_3CO)_2O \longrightarrow [(C_6H_5)_2CHCO]_2O + 2CH_3COOH \quad (36)$$

To a flask containing 50 gm (0.236 mole) of diphenylacetic acid is added 50 gm (0.49 mole) of acetic anhydride and the solution refluxed for 2 hr. The excess acetic anhydride is removed by distillation and the thick brown liquid residue is treated with ether to cause crystallization of the anhydride product. The crystals are filtered, washed with cold ether, and dried to afford 43–44 gm (90–92%), m.p. 98°C. The product can also be distilled at 182°C (3.0 mm Hg).

## TABLE X

### PREPARATION OF CARBOXYLIC ANHYDRIDES BY THE REACTION OF CARBOXYLIC ACIDS WITH ACETIC ANHYDRIDE

| Carboxylic acid (moles) | Acetic anhydride (moles) | Catalyst | Reaction conditions Temp. (°C) | Reaction conditions Time (hr) | Anhydride yield (%) | B.p., °C (mm Hg) | M.p. (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|
| $C_6H_5COOH$ (12.3) | 14.7 | $H_3PO_4$ (1.0 g) | 120 | — | 72–74 | — | 43 | *a* |
| 3-Nitrophthalic acid (1.0) | 2.0 | — | 136 | 1/2 | 88–93 | — | 163–164 | *b* |
| Homophthalic acid (0.33) | 0.33 | | 136 | 2 | 85–88 | — | 140–141 | *c* |
| Diphenic acid (0.21) | 0.73 | — | 120 | 1 | 97 | — | 217 | *d* |
| Diphenylacetic acid (0.236) | 0.49 | — | 136 | 2 | 90–92 | 182 (3) | 98 | *e* |
| Benzylsuccinic acid (0.33) | 0.49 | — | 136 | 1/4 | 90–95 | 185 (2) | 95–97 | *f* |
| α-*n*-Butylglutaric acid (1.0) | 9.2 | — | 136 | 3/4 | 76 | 170–172 (12) | — | *g* |
| α-*n*-Hexylglutaric acid (1.0) | 10.6 | — | 136 | 3/4 | 80 | 195–197 (14) | — | *g* |
| α-*n*-Heptylglutaric acid (1.0) | 11.3 | — | 136 | 3/4 | 67 | — | 36 | *g* |
| α-Phenylglutaric acid (1.0) | 2.7 | — | 136 | 1 | 82–86 | — | 90–94 | *h* |
| Capric acid (1.0) | 3.0 | — | 136 | 6–8 | 50–80 | — | 24.7 | *c* |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Lauric acid (1.0) | 3.0 | — | 136 | 6–8 | 50–80 | — | 42.1 | *i* |
| Myristic acid (1.0) | 3.0 | — | 136 | 6–8 | 50–80 | — | 53.5 | *i* |
| Palmitic acid (1.0) | 3.0 | — | 136 | 6–8 | 50–80 | — | 63.9 | *i* |
| Stearic acid (1.0) | 3.0 | — | 136 | 6–8 | 50–80 | — | 70.7 | *i* |
| *d*-Tartaric acid (0.27) | 1.33 | $H_2SO_4$ (1.2 ml) | 136 | 1/6 | 71–77 (diacyl-*d*-tartaric anhydride) | — | 133–134 | *j* |
| Adipic acid (0.69) | 3.17 | — | 136 | 4–6 | — (polymeric adipic anhydride) | — | 73–75 | *k* |
| Pivalic acid (0.49) | 0.88 | — | 120 | 1–2 | 39 | 78 (12)<br>192–194 (760) | —[n] | *l* |
| *cis,cis,cis,cis*-1,2,3,4-Cyclopentanetetracarboxylic acid (1.0) | 4.0 | — | 136 | 1–2 | — | — | — | *m* |

---

[a] H. T. Clarke and E. J. Rahrs, *Org. Syn. Coll.* **1**, 91 1932). [b] B. H. Nicolet and J. A. Bender, *Org. Syn. Coll.* **1**, 410 (1932). [c] O. Grummitt, R. Egan, and A. Buck, *Org. Syn. Coll.* **3**, 449 (1955). [d] R. C. Roberts and T. B. Johnson, *J. Amer. Chem. Soc.* **47**, 1396 (1925). [e] C. D. Hurd, R. Christ, and C. L. Thomas, *J. Amer. Chem. Soc.* **55**, 2589 (1933). [f] W. F. Beech and N. Legg, *J. Chem. Soc.* 1887 (1949). [g] J. C. Roberts and B. Shaw, *J. Chem. Soc.* 2842 (1950). [h] E. C. Horning and A. F. Finelli, *Org. Syn. Coll.* **4**, 790 (1963). E. C. Horning and A. F. Finelli, *J. Amer. Chem. Soc.* **71**, 3204 (1949). [i] J. M. Wallace, Jr., and J. E. Copenhaver, *J. Amer. Chem. Soc.* 63, 699 (1941). [j] R. L. Shriner and C. L. Furrow, Jr., *Org. Syn. Coll.* **3**, 242 (1963). [k] J. W. Hill, *J. Amer. Chem. Soc.* **52**, 4110 (1930). [l] M. F. Ansell, M. A. Davis, J. W. Hancock, W. J. Hickinbottom, P. G. Holton, and A. A. Hyatt, *J. Chem. Soc.* 2705 (1955). [m] R. V. Volkenburgh, J. R. Olechowski, and G. C. Royston, U.S. Patent 3,194,816 (1965). [n] $n_D$ 1.4089 (20°C).

### *3-4. Preparation of Benzoic Anhydride* [18]

$$2C_6H_5COOH + (CH_3CO)_2O \longrightarrow (C_6H_5CO)_2O + 2CH_3COOH \qquad (37)$$

To a three-necked flask equipped with a mechanical stirrer, dropping funnel, fractionating column, and distillation head is added 150 gm (1.23 moles) of benzoic acid, 150 gm (1.47 moles) of acetic anhydride, and 0.1 gm of sirupy phosphoric acid. The mixture is stirred, heated, and distilled slowly, keeping the head temperature at 120°C or below. After 25 ml of distillate is removed another 25.0 gm (0.245 mole) of acetic anhydride is added and the distillation continued until the temperature of the reaction mixture in the flask reaches 270°C. The residue is distilled under reduced pressure to afford a fraction b.p. 210–220°C (19–20 mm Hg) which weighs 110–120 gm. Recrystallization of the crude benzoic anhydride from benzene–petroleum ether affords 100–103 gm (72%) of pure anhydride, m.p. 43°C.

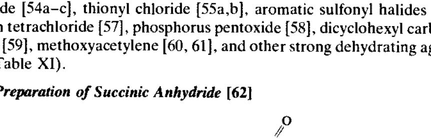
For earlier references to this method see Autenrieth [51] and Autenrieth and Thomae [52].

Maleic anhydride can be prepared by heating maleic acid in xylene with acetic anhydride [52b]. The use of other anhydrides in place of acetic anhydride is also described.

## C. Miscellaneous Dehydrating Methods

Dehydration of acids to give anhydrides can also be accomplished by heating the dibasic acid with either trifluoroacetic anhydride [53], acetyl chloride [54a–c], thionyl chloride [55a,b], aromatic sulfonyl halides [56], silicon tetrachloride [57], phosphorus pentoxide [58], dicyclohexyl carbodiimide [59], methoxyacetylene [60, 61], and other strong dehydrating agents (see Table XI).

### *3-5. Preparation of Succinic Anhydride* [62]



(38)

To a flask equipped with a reflux condenser topped with a tube leading to an HCl trap is added 118 gm (1.0 mole) of succinic acid and 235 gm (215 ml, 3.0 moles) of acetyl chloride. The contents are refluxed for 2–3 hr, cooled, the anhydride filtered, washed twice with 75 ml of cold

## TABLE XI

ANHYDRIDES BY THE REACTION OF MISCELLANEOUS DEHYDRATING AGENTS WITH CARBOXYLIC ACIDS[h]

| Carboxylic acid (moles) | Dehydrating agent (moles) | Solvent (ml) | Reaction conditions Temp. (°C) | Time (hr) | Anhydride yield (%) | B.p., °C (mm Hg) or m.p., °C | Ref. |
|---|---|---|---|---|---|---|---|
| Benzoic<br>(0.1) | $C_6H_5SO_2Cl$<br>(0.06) | Pyridine<br>(20) | 25 | 1/12 | 74 gm | 41.5–42.5 | *a* |
| 3,4,5-Trimethoxybenzoic<br>(0.58) | $SOCl_2$<br>(0.43) | Ether<br>(800) | | | | | |
| | | Pyridine<br>(75) | 0 | 2–3 | 51 | 159–160 | *b* |
| Anisic<br>(0.67) | $SOCl_2$<br>(0.43) | Pyridine<br>(75) | 0 | 2–3 | Anisic Acid<br>75 gm | 98–99 | *b* |
| Phenylsuccinic<br>(0.74) | $CH_3COCl$<br>(3.5) | — | — | 1 | 80 | 190–194 (6)<br>53–54 | *c* |
| Succinic<br>(1.0) | $CH_3COCl$<br>(3.0) | — | 51 | $1\frac{1}{2}$–2 | 93–95 | 118–119 | *d* |
| (2.0) | $POCl_3$<br>(1.0) | — | 105 | 1 | 82–96 | 255–260 (760)<br>119–120 | *e* |
| Dibutylmalonic<br>(0.031) | $(CF_3CO)_2O$<br>(0.031) | Ether<br>(35) | 25 | 1/6 | 98 | — | *f* |
| $CF_3COOH$<br>(1.0) | $P_2O_5$<br>(0.87) | — | 72 | 1 | 74 | 39 | *g* |
| EtCOOH | $CH_3SO_2Cl$<br>$Et_3N$ | THF | −15 | 1 | 85 | | *i* |

[a] J. H. Brewster and C. J. Ciotti, Jr., *J. Amer. Chem. Soc.* **77**, 6214 (1955). [b] T. Heap and R. Robinson, *J. Chem. Soc.* 67 (1929). [c] C. C. Price and A. J. Tomisek, *J. Amer. Chem. Soc.* **65**, 439 (1943). [d] L. F. Fieser and E. L. Martin, *Org. Syn. Coll.* **2**, 560 (1943). [e] R. L. Shriner and H. C. Struck, *Org. Syn. Coll.* **2**, 560 (1943). [f] A. C. Duckworth, *J. Org. Chem.* **27**, 3146 (1962). [g] E. J. Bourne, M. Stacey, J. C. Tatlow, and J. M. Tedder, *J. Chem. Soc.* 2976 (1949). [h] See Refs. *d* and *e* for further references to earlier work on the use of other dehydrating agents such as succinyl chloride, phosphorus pentachloride or phosphorus pentoxide. [i] A. Nangia, and S. Chandragekaran. *J. Chem. Res. Synop*, (3) 100 (1984); *Chem. Abstr.* **101**, 6586w (1984).

ether, and dried under reduced pressure to afford 93–95 gm (93–95%), m.p. 118–119°C.

This method is more convenient than that using phosphorus oxychloride since lower temperatures are used and the product does not have to be distilled.

### 3-6. *Preparation of Benzoic Anhydride* [63]

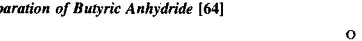
$$2C_6H_5COOH + C_6H_5SO_2Cl + C_5H_5N \longrightarrow (C_6H_5CO)_2O + C_6H_5SO_3H + C_5H_5N\cdot HCl \qquad (39)$$

To a flask containing 12.0 gm (0.1 mole) of benzoic acid in 20 ml of pyridine is added slowly with stirring 8.8 gm (0.05 mole) of benzenesulfonyl chloride. The temperature rises to about 75°C. After the addition the mixture is stirred for 5–10 min, poured into 50 gm of ice in 100 ml of water. The oil that separates is scratched to induce crystallization, then filtered, washed with ice water, and dried to afford 10 gm (97%), m.p. 39–40°C.

$$2RCOOH + CH_3OC{\equiv}CH \longrightarrow CH_3COOCH_3 + (RCO)_2O \qquad (40)$$

The use of methoxyacetylene is claimed to require the mildest conditions for converting a dicarboxylic acid into its anhydride (Eq. 37). For example, heptanoic, phenylacetic, $\beta$-phenylpropionic, maleic, acrylic, chloroacetic, and trichloroacetic acids all afforded their anhydrides at or below room temperature. The use of phosphoric acid and mercuric oxide as catalysts allowed crotonic and pivalic acids to react readily at room temperature. Cinnamic and palmitic acids failed to give the anhydride, possibly because of their low solubility in the reaction media. Arens and Modderman [61] have earlier shown that cinnamic acid reacts readily with ethoxyacetylene without added catalysts in an ether solution to afford cinnamic anhydride in 77% yield (see Table XII). It appears that ethoxyacetylene is a much more reactive starting material since no added catalysts are required. Formic acid does not afford formic anhydride but only carbon monoxide. Some examples illustrating the usefulness of this latter method are described in Table XII.

### 3-7. *Preparation of Butyric Anhydride* [64]



$$2C_3H_7COOH + CH_3OC{\equiv}CH \xrightarrow[10^\circ C]{} (C_3H_7CO)_2O + CH_3O\overset{\overset{\displaystyle O}{\|}}{C}{-}CH_3 \qquad (41)$$

To a cooled flask containing 88 gm (1.0 mole) of $n$-butyric acid at 10°C is added dropwise 28.0 gm (0.5 mole) of methoxyacetylene over a 1-hr period. After stirring the reaction mixture for 16 hr at 20°C the contents

TABLE XII

REACTION OF ALKOXYACETYLENES WITH CARBOXYLIC ACIDS TO AFFORD ANHYDRIDES

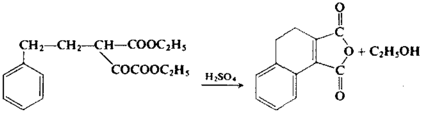
| Carboxylic acid (moles) | Acetylene (moles) | Solvent (ml) | Catalyst (ml) | Reaction conditions Temp. (°C) | Reaction conditions Time (hr) | Anhydride yield (%) | B.p., °C (mm Hg) or m.p., °C | $n_D$ (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | Methoxy-acetylene | | | | | | | | |
| Acetic (0.1) | 0.05 | — | — | 0 | 1½ | 85 | 71–72 (70) | 1.3906 (85) | *a* |
| Butyric (0.1) | 0.05 | — | — | 0<br>26 | 1<br>20 | 61 | 91–92 (18) | 1.4118 (25) | *a* |
| Monochloroacetic (0.1) | 0.05 | THF (10) | | 15 | 18 | — | 181–120 (0.05) | | *a* |
| Trichloroacetic (0.0086) | 0.009 | $CH_2Cl_2$ (4) | — | 20 | 20 | 64 | 128 (0.02) | 1.5078 (20.5) | *a* |
| Heptanoic (0.01) | 0.0073 | — | — | 20 | 20 | 67 | 145 (0.01) | 1.4341 (20) | *a* |
| Phenylacetic (0.01) | 0.009 | $CH_2Cl_2$ (2) | — | 20 | 18 | 96 | 72–72.5 | | *a* |
| β-Phenyl propionic (0.01) | 0.009 | $CH_2Cl_2$ (2) | — | 20 | 18 | 53 | 195 (0.05) | 1.5419 (20) | *a* |
| Pivalic (0.01) | 0.0073 | Ether (2) | $H_3PO_4$ (0.05) | 20 | 16 | 75 | 103 (15) | 1.4104 (19.5) | *a* |
| Crotonic (0.01) | 0.009 | $CH_2Cl_2$ (2) | HgO (Trace) | 20 | 20 | 100 | 95 (0.02) | 1.466 (17) | *a* |
| | Ethoxy-acetylene | | | | | | | | |
| Maleic (0.01) | 0.014 | $CH_2Cl_2$ (5) | — | 25–30 | 1 | 95 | 51–52 | — | *a* |
| Acetic (0.22) | 0.11 | Ether (20) | — | 35–36 | 1/2 | 63 | — | — | *b* |
| Benzoic (0.20) | 0.10 | Ether (20) | — | 35–36 | 1/2 | — | 41.5–42.5 | — | *b* |
| Cinnamic (0.008) | 0.11 | Ether (20) | — | 35–36 | 1/2 | 77 | — | — | *b* |

[a] G. Eglinton, E. R. H. Jones, B. L. Shaw, and M. C. Whiting, *J. Chem. Soc.* 1860 (1954).

[b] J. F. Arens and P. Modderman, *Proc. Koninkl. Nederland. Akad. Wetenschap.* **53**, 1163 (1950).

are distilled to afford the following three fractions: (1) b.p. 56°C, $n_D^{19}$ 1.3628, 23 gm (62%), methyl acetate; (2) b.p. 72–73°C (18 mm Hg), $n_D^{24}$ 1.3990, 10.0 gm (11%), butyric acid; (3) b.p. 91–92°C (18 mm Hg), $n_D^{25}$ 1.4118, 48.0 gm (61%), butyric anhydride.

The dehydration of esters to give anhydrides has earlier been reported by Kraut for preparation of succinic anhydride by the reaction of ethyl succinate with benzoyl chloride [65]. A related method has been used for the preparation of 3,4-dihydro-1,2-naphthalic anhydride by the reaction of ethyl α-ethoxalyl-γ-phenylbutyrate with concentrated sulfuric acid (Eq. 39) [66].



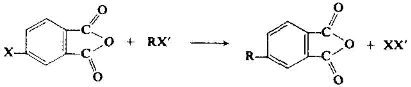
(42)

## 4. REACTION OF ANHYDRIDES TO GIVE SUBSTITUTED ANHYDRIDES

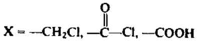
Anhydrides undergo condensation, substitution, oxidation, and reduction reactions to give a variety of anhydride structures.

### A. Condensation Reactions

Anhydrides containing a reactive functional group may be condensed with other compounds but under mild conditions in order to preserve the anhydride structure. See, for example, Eq. (43) [67, 68].



(43)

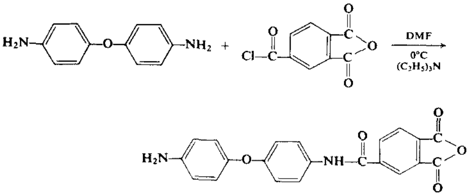


$X = -CH_2Cl,\ -\overset{\overset{O}{\|}}{C}-Cl,\ -COOH$

$X' = -NH_2, -OH, COOH, -COCl, NCO$ [69]

A specific example is the use of trimellitic anhydride acid chloride to react with diprimary amines to give derivatives useful for the production of polyimides [67].

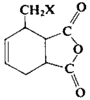
### *4-1. Preparation of the 3-Oxydianilide of Trimellitic Anhydride* [67]



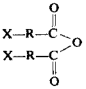
(44)

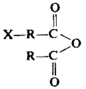
To a cooled flask containing 20.0 gm (0.10 mole) of oxydianiline and 10.1 gm (0.10 mole) of triethylamine in 100 ml of DMF at 0°C is added dropwise with stirring a solution of 21.1 gm (0.10 mole) of trimellitic anhydride acid chloride in 100 ml of DMF at such a rate to keep the pot temperature at 0–5°C. After the addition, the stirring is continued for 2 hr, the reaction mixture poured with stirring into 500 ml of ice water, and the precipitated product quickly filtered, rinsed with cold methanol, and dried under reduced pressure to afford 38.0 gm (100%) of a gray solid, m.p. > 335°C.

In place of trimellitic anhydride derivatives, other cyclic and acyclic anhydrides may be used, such as the following:



[70]

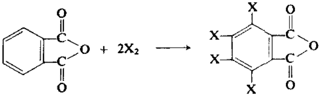




X = halogen, -COCl, -COOH, -OH, or -CH₂X.

### B. Substitution and Addition Reactions

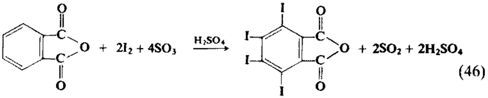
The reaction of phthalic anhydride with halogens affords tetrahalophthalic anhydrides (Eq. 45).



(45)

X = Cl [71], Br, I [72a, b]

### 4-2. *Preparation of Tetraiodophthalic Anhydride* [72a]


(46)

**CAUTION:** This reaction should be carried out in a well-ventilated hood.

To a flask equipped with a mechanical stirrer and an air condenser topped with a tube leading to a gas trap is added 74.0 gm (0.5 mole) of phthalic anhydride, 162 gm (0.638 mole) of iodine, and 300 ml of 60% fuming sulfuric acid (1.84 moles). The flask is gently heated to 45–50°C, at which point the reaction commences. If the reaction becomes too vigorous it may be necessary to use a ice bath to lower the temperature to 40–50°C. The reaction mixture is eventually (4 hr) heated up to 65°C until all visible reaction has ceased. The reaction mixture is cooled to 10–20°C and an additional 81.0 gm (0.318 mole) of iodine is added and the reaction again slowly heated up to 65°C (1½ hr) and again when the reaction ceases it is cooled. Another 27.0 gm (0.107 mole) of iodine is added and the reaction is again heated up to 65°C (1 hr). The flask is heated with an oil bath to a bath temperature of 175–180°C, at which point the sulfur trioxide and iodine fumes evolve. After about 2 hr, when the gaseous evolution ceases, the flask is cooled to about 60°C and the mxiture then poured into a beaker of water. The contents are allowed to stand overnight at room temperature, filtered, washed with two 50-ml portions of conc. sulfuric acid and then with three 100 ml portions of water. The light yellow crystalline product is put into a beaker containing 1 liter of water and 10 gm of sodium bisulfite in order to remove the last traces of free iodine. The aqueous solution is decanted, the product washed five times with ½ liter of water, washed twice with 100 ml of acetone and then dried at 60°C to afford 260–268 gm (80–82%), m.p. 327–328°C.

No suitable solvent for recrystallization has been reported.

It has been shown that thiols add to α,β-unsaturated aldehydes such as maleic anhydride to give the corresponding substituted mercaptoanhy-

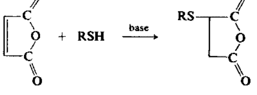
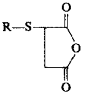
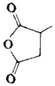

(47)

TABLE XIII

ADDITION OF RSH TO MALEIC ANHYDRIDE TO AFFORD *dl*-ALKYLTHIO- AND ARYLTHIOSUCCINIC ANHYDRIDES[a]



| R = | B.p., °C (mm Hg) or m.p., °C[a] | Yield (%) | R = | B.p., °C (mm Hg) or m.p., °C[a] | Yield (%) |
|---|---|---|---|---|---|
| $CH_3$ | 142 (2) | 64 | *p*-$CH_3C_6H_4$ | 155–160 (0.01)[d] | 65 |
| *n*-$C_4H_9$ | 122–124 (0.3) | 89 | *p*-$ClC_6H_4$ | 96–98[k] | 97 |
| *tert*-$C_4H_9$ | 83.5–84.5[b] | 41 | *p*-$CH_3OC_6H_4$ | —[g] | 45[h] |
| *n*-$C_8H_{17}$ | 175–179 (0.6) | 89 | *p*-$AcNHC_6H_4$ | 186–188 (dec.)[l] | 77 |
| *n*-$C_{12}H_{25}$ | 42–43[c] | 94 | *p*-$O_2NC_6H_4$ | 114–115[m] | 90 |
| *tert*-$C_{12}H_{25}$ | 160–170 (0.01)[d] | 60 | *o*-$O_2NC^9H_4$ | 124–125[m] | 96 |
| —$CH_2CH_2$ | 128–130[c] | 42[f] | $C_6Cl_5$ | 166–168[n] | 87 |
| $C_2H_5OOCCH_2$ | 140–145 (0.2) | 76 | | | |
| $HOOCCH_2$ | —[g] | 100[h] | | | |
| $C_6H_5CH_2$ | 150–155 (0.03)[d] | 88 |  | —[g] | 90 |
| $C_6H_5$[c] | 176–178 (1.5) | 88 | | | |

[a] All melting points and boiling points are uncorrected. [b] Recrystallized from carbon tetrachloride. [c] From petroleum ether; M. L. Szabo and E. T. Stiller, *J. Amer. Chem. Soc.* **70**, 3667 (1948) reported m.p. 45°–46°C. [d] Distilled in short path still; ranges are air bath temperatures. [e] Washed with chloroform. [f] Yield of crude product was 100%. [g] Decomposed on attempted distillation. [h] Yield of crude material. [i] Oil, very soluble in benzene. [j] Solid. Soluble in benzene. [k] From toluene; soluble in acetone. [l] From dioxane. [m] From glacial HOAc–$Ac_2O$. [n] From acetone. Also recrystallizes from benzene. [Adapted from F. B. Zienty, B. D. Vineyard, and A. A. Schleppnik, *J. Org. Chem.* **27**, 3140 (1962). Copyright 1962 by the American Chemical Society. Reprinted by permission of the copyright owner.]

drides as shown in Eq. 47 and Table XIII. The reaction is base catalyzed, and anhydrous conditions are used. Lewis acids such as boron trifluoride and sulfuric acid do not catalyze the reaction, and the use of peroxides [73] affords only poor yields of the addition product.

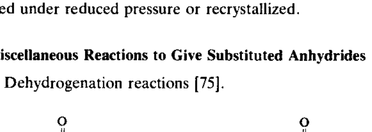
The addition of other substituents to the double bond of unsaturated anhydrides is also possible.

### *4-3. General Method for the Preparation of Mercaptoanhydrides* [74]

A flask containing 9.8 gm (0.1 mole) of maleic anhydride in 100 ml of dioxane is heated to 65°C. Then 0.74 gm (0.005 mole) of triethylenediamine and 0.10 mole of the thiol is added. A slight exotherm of a few degrees is noticed within about 5 min, and the reaction mixture is held at 65°C for $\frac{1}{2}$–1 hr. Approximately 0.005–0.01 mole of conc. sulfuric acid is added, the solvent is removed by distillation, and the product is either distilled under reduced pressure or recrystallized.

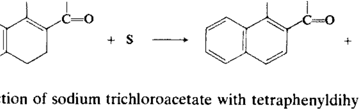
## C. Miscellaneous Reactions to Give Substituted Anhydrides

(1) Dehydrogenation reactions [75].



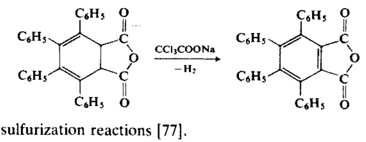
(48)

(2) Reaction of sodium trichloroacetate with tetraphenyldihydrophthalic anhydride produced only the dehydrogenated product, tetraphenylphthalic anhydride [76] (Eq. 49).



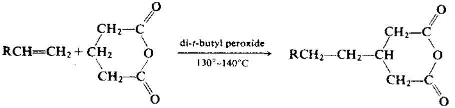
(49)

(3) Desulfurization reactions [77].



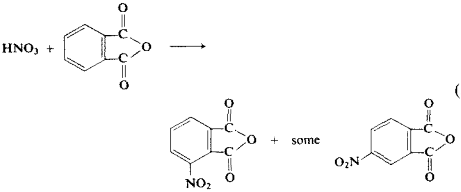
(50)

(4) Alkylation of cyclic anhydrides with olefins by heating with organic peroxides [78] (Eq. 51).



(51)

(5) Nitration of phthalic anhydride [79] (Eq. 52).

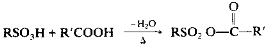


(52)

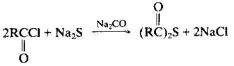
## 5. SULFONIC ANHYDRIDE, MIXED SULFONIC-CARBOXYLIC ANHYDRIDES, AND THIOLANHYDRIDES

Anhydrides can be prepared from sulfonic acids [79b,c] and from mixed sulfonic and carboxylic acids [79d,e]. Thiolanhydrides are prepared by the reaction of the carboxylic acid chloride with Na$_2$S [79a,f,g,h].

$$2RSO_3H \xrightarrow[\Delta]{-H_2O} (RSO_2)_2O \qquad (53)$$



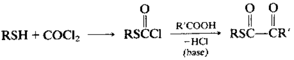
$$RSO_3H + R'COOH \xrightarrow[\Delta]{-H_2O} RSO_2\,O-\overset{\overset{O}{\|}}{C}-R' \qquad (54)$$



$$2R\underset{\underset{O}{\|}}{C}Cl + Na_2S \xrightarrow{Na_2CO} (R\overset{\overset{O}{\|}}{C})_2S + 2NaCl \qquad (55)$$

A typical preparation of each is described in Table XIV.

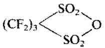
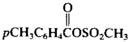
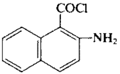
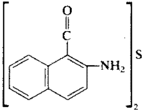
A variation is the preparation of alkylthiol/carbonic anhydrides, as described by Stanley and Tarbel [79i].



$$RSH + COCl_2 \longrightarrow RS\overset{\overset{O}{\|}}{C}Cl \xrightarrow[\substack{-HCl \\ (base)}]{R'COOH} RS\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}R' \qquad (56)$$

## TABLE XIV

### PREPARATION OF SULFONIC ANHYDRIDE, MIXED SULFONIC–CARBOXYLIC ANHYDRIDES AND THIOLANHYDRIDES

| $RSO_3H$ | Dehydrating agent | RCOCl or $(RCO)_2O$ | $Na_2S$ or $H_2S$ | Temp. °C | Time (min) | Product (b.p. °C $n_D$) | Ref. |
|---|---|---|---|---|---|---|---|
| $R_f(SO_3H)_2$ | $P_2O_5$ | | | 130 | | <br>b.p. 109–110<br>$n_D^{32}$ 1.3562 | *a* |
| $CH_3SO_3H$ | — | $(p\text{-}CH_3C_6H_4CO)_2O$ in $CH_3NO_2$ | — | 30–40 | 20 | <br>$pCH_3C_6H_4\overset{O}{\overset{\parallel}{C}}OSO_2CH_3$ | *b* |
| — | — |  | $H_2S$ + pyridine | 10 | |  | *c* |
| | | | | 80 | 480 | | |

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[a] F. E. Behr, U.S. Pat. 4,329,478 (1982). [b] K. E. Wiegand, U.S. Pat. 4,008,271 (1976). [c] S. R. Mirviss, U.S. Pat. 3,755,440 (1973).

## 6. MISCELLANEOUS METHODS

(1) Preparation of benzoic, acetic, and propionic anhydrides by the reaction of bromine with the sodium salts of the respective acids in the presence of sulfur [80].

(2) Preparation of *n*-caproic anhydride by the reaction of a mixture of sodium caproate and sulfur with chlorine [81].

(3) Reaction of toluene, nickel tetracarbonyl, benzoyl peroxide, and carbon monoxide at 325°C for 2 hr to afford 62% phthalic anhydride [82].

(4) Reaction of bromobenzene, sodium carbonate, nickel tetracarbonyl with carbon monoxide at 325°C for 2 hr to afford 73% phthalic anhydride [83].

(5) Preparation of symmetrical anhydrides of hydroxy acids [84].

(6) Preparation of anhydrides from the reaction of 1-methoxyvinyl esters [85].

(7) Mixed sulfonic–carboxylic anhydrides [86a,b].

(8) Carbonic–phosphoric and carbonic–carboxylic anhydrides [87].

(9) Preparation of *p*-nitrobenzoic *t*-butyl thiolcarbonic anhydride [88].

(10) Preparation of citraconic anhydride from itaconic anhydride [89].

(11) Preparation of citraconic anhydride from citric acid [90a–d].

(12) Preparation of citraconic anhydride from lactic acid [91].

(13) Preparation of citraconic anhydride from hydroxypyrotartaric acid [92].

(14) Polymerization of *N*-carboxyanhydrides [93].

(15) Reaction of acid chlorides with esters to give anhydrides [94].

(16) Reaction of carbon monoxide with organomercury compounds in the presence of palladium acetate in nonhydroxylic solvents [95].

(17) Catalytic oxidation of aldehydes to anhydrides [96a–c].

(18) Catalytic oxidation of olefin hydrocarbons to anhydrides [97].

(19) Oxidation of aromatic hydrocarbons to anhydrides [98a–c].

(20) Acyl transfer in the reaction of acyl halides with anhydrides (transacylation reaction) [99].

(21) Preparation of benzoic anhydride from benzoyl chloride and lead nitrate [100].

(22) Preparation of benzoic anhydride from benzoyl chloride and potassium pyrosulfite [101].

(23) Preparation of benzoic anhydride from benzoyl chloride and sodium carbonate [102a,b]

(24) Preparation of benzoic anhydride by the reaction of benzotrichloride and sulfuric acid [103].

(25) Preparation of benzoic anhydride by the reaction of benzoic acid with phosphorus in benzene solution by shaking with air or oxygen [104].

(26) Benzoic anhydride from the reaction of diphenyldichloromethane and sodium benzoate [105].

(27) Succinic anhydride from benzophenone dichloride and barium or sodium succinate [105].

(28) Succinic anhydride from succinyl chloride and oxalic acid [106].

(29) Succinic anhydride from succinyl chloride and sodium acetate [107].

(30) Thermal isomerization of polycrystalline *exo*- and *endo*-5-norbornene-2,3-dicarboxylic anhydrides [108].

(31) Reaction of ynamines with carboxylic acids to yield carboxylic anhydrides [109].

(32) The preparation of 6,6′-diethynyldiphenic anhydride [110].

(33) Preparation of 3,6-diethylphthalic anhydride by the reaction of 2,5-diethylfuran with maleic anhydride and subsequent reaction with sulfuric acid [111].

(34) A novel route to bicyclo[2.2.2]octenetetracarboxylic acid dianhydrides [112].

(35) Preparation of methanesulfonic anhydride by reaction of methanesulfonic acid and phosphorus pentoxide at 0°C [113].

(36) Preparation of tetrafluorocyclobutanedicarboxylic anhydride [114].

(37) Preparation of carboxylic anhydrides by reaction of sodium salts of carboxylic acids with carbon tetrachloride [115].

(38) Mono and polyanhydrides via reaction of 2,2,4,4,6,6-hexachlorotriazotriphosphorine with carboxylic acids under mild conditions [116].

(39) Preparation of propionic anhydride by the reaction of propionic acid with ethylene and carbon monoxide in the presence of catalysts [117].

(40) Carbonylation of methylacetate to give acetic anhydride [118].

(41) A one-pot synthesis of carboxylic anhydrides from carboxylic acids and *N,N,N′,N′*-tetramethylchloroformamidinium chloride under mild conditions [119].

(42) Catalysts for the preparation of aromatic carboxylic anhydrides [120].

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# CHAPTER 3/MONOALKYL SULFATES

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## 1. INTRODUCTION

Alkyl sulfates are usually prepared by the reaction of alcohols with $SO_3$ or its derivatives and by the reaction of unsaturated compounds with sulfuric acid.

This chapter is mainly concerned with methods of synthesis of sodium alkyl sulfates derived from alcohols. These compounds are useful as detergents and also have biological and biochemical importance. Sulfates are also synthesized in living systems, and their preparation is of interest in medicinal chemical research.

SCHEME 1

Methods of Synthesizing Monoalkyl Sulfates

$$\begin{tikzcd}
 & \mathrm{ROH + ClSO_3H} \arrow[d, "-\mathrm{HCl}"] & \\
\mathrm{ROH + SO_3} \arrow[r] & \mathrm{ROSO_3H} & \mathrm{ROH + H_2SO_4} \arrow[l, "-\mathrm{H_2O}"'] \\
 & \mathrm{ROH + SO_3 \cdot complex} \arrow[u] &
\end{tikzcd}$$

The most important methods of synthesizing sodium alkyl sulfates or monoalkyl sulfates are summarized in Scheme 1.

A less often used but important method for sulfating unsaturated alcohols is the use of sulfamic acid, as shown in Eq. 1.

$$\mathrm{ROH + HSO_3NH_2 \longrightarrow ROS\bar{O}_3\overset{+}{N}H_4} \tag{1}$$

Sulfur trioxide complexes have gained important industrial use in sulfating dyes, carbohydrates, sterols, and other sensitive heterocyclic compounds.

The nomenclature of the sulfate esters and their salts follows the *Chemical Abstracts* system [1]. The following two compounds are examples:

| $n\text{-}C_{12}H_{25}OSO_3H$ | $n\text{-}C_{12}H_{25}OSO_3Na$ |
|---|---|
| *n*-Dodecyl sulfate or lauryl sulfate | Sodium *n*-dodecyl sulfate or sodium lauryl sulfate |
| (I) | (II) |

Sulfate esters and their sodium salts have relatively good stability except for those derived from tertiary alcohols [2] or partially esterified alcohols [3], such as ethylene glycol monolaurate. Sodium alkyl sulfates hydrolyze under acid [4] as well as basic conditions [5] in aqueous solution at elevated temperatures. Basic hydrolysis of ethyl and propyl sulfates gave no detectable olefin formation, but isopropyl and isobutyl sulfates afford minor amounts of olefins [5]. Neopentyl and pinacolyl sulfates involve complete rearrangement during basic hydrolysis; isobutyl sulfate involves partial rearrangement and 1-ethylpropyl sulfate hydrolyzes without rearrangement [5]. *sec*-Butyl sulfate hydrolyzes with inversion of configuration accompanied by only a small amount of racemization [5a].

The methods of synthesis are discussed according to the reagent used, and several miscellaneous methods are described in Section 3.

Sulfation of fatty alcohols and polyalkoxylates is the basis of commercial detergents and emulsifiers, which amounted to 111,000 metric tons in 1980.

Linear ethoxylates are used as the raw material for ether sulfates used in the production of biodegradable detergent formulations.

A brief review of sulfation by Knaggs, Nussbaum, and Schultz is worth consulting [5b].

## 2. SULFATION OF ALCOHOLS

As noted in the introduction section, the five most important methods of sulfating alcohols involve the use of either sulfur trioxide, sulfur trioxide complexes, chlorosulfonic acid, sulfuric acid, or sulfamic acid. Chlorosulfonic acid is often used in the laboratory but has the disadvantage that in some cases the last traces of hydrogen chloride are difficult to remove. Sulfur trioxide tends to give pure products but may cause charring or colored products unless special precautions are taken. Sulfur trioxide complexes are relatively easy to prepare, and for some, the sulfation reactions can even be carried out in aqueous solution. This sulfation process is particularly important for unsaturated and acid-sensitive compounds.

In some cases, the amine complexes leave a difficult-to-remove amine odor. Sulfuric acid is used without any problems for most saturated primary alcohols, but oleum gives poor yields and poor color with some (tridecyl alcohol). Sulfamic acid is often used for acid-sensitive alcohols, but the reaction also requires elevated temperatures (125–145°C) to give the ammonium salt.

*Each of these processes for the preparation* of monoalkyl sulfates is discussed in detail in the following sections.

A comparison of some of the methods for the sulfation of four representative alcohols is shown in Table I.

The data in Table I tend to indicate that in most cases, sulfur trioxide and chlorosulfonic acid give sodium alkyl sulfates in the highest yields and of the greatest purity.

Thionyl chloride when added to sulfuric acid was reported to promote sulfate ester formation [5c].

### A. Sulfuric Acid

*Sulfuric acid reacts with primary and secondary* alcohols by a bimolecular displacement reaction with no alkyl-oxygen fission [2]. The mechanism of the reaction is similar to the acid-catalyzed esterification of carboxylic

TABLE I
SULFATION OF ALCOHOLS

| Alcohol ROH, R = | Sulfating agent (approx. 1.0 mole/ mole alcohol) | Yield as $ROSO_3Na$ (%) | Purity (%) | Ref. |
|---|---|---|---|---|
| Lauryl | $ClSO_3H$ | 86–90 | 98 | *a* |
| | $SO_3$ | 74 | 98 | *a* |
| | Oleum (20%) | 91 | 80–90 | *a* |
| | $H_2SO_4$ (conc.) | 49 | 60–70 | *a* |
| | $SO_3$-pyridine | 50 | 90 | *a* |
| | $H_2N—SO_3H$ | 30 | 80–90 | *a* |
| Hecadecyl | $ClSO_3H$ | 98 | 97 | *b* |
| | $SO_3$ | 97 | 97 | *b* |
| | Oleum (20%) | 90 | 96 | *b* |
| | $H_2SO_4$ (conc.) | 70 | 91 | *b* |
| Tridecyl | $ClSO_3H$ | 97 | 86 | *c* |
| | $SO_3$ | 97–99 | 86 | *c* |
| | Oleum (20%) | (Poor yield & color) | | *c* |
| | $H_2N—SO_3H$ | (Poor yield & color) | | *c* |
| Ethoxylated tridecyl (4 moles ethylene oxide) | $ClSO_3H$ | 93 | 81 | *c* |
| | $SO_3$ | 95 | 51 | *c* |
| | Oleum (20%) | 94 | 57 | *c* |
| | $H_2N—SO_3H$ | 99 | 72 | *c* |

[a] Author's Laboratory (S.R.S.). [b] Enjay Chem. Co., Tech. Infor. Sheet, DC-1 (date unknown). [c] Enjay Chem. Co., Tech. Bull. C-21 (1960).

acids. Sulfation of optically active 2-butanol gives a sulfate ester with complete retention of configuration [2]. In addition, neopentyl alcohol sulfates without rearrangement [2].

Kinetic data indicate that primary alcohols, including neopentyl alcohol, were sulfated at comparable rates and were sulfated about 10 fold-faster than the secondary alcohols [2]. The kinetics followed the following rate expression:

$$\frac{d[\mathrm{ROSO_3H}]}{dt} = k[\mathrm{ROH}][\mathrm{H_2SO_4}][\mathrm{H^+}\ \text{activity}]$$

Equilibrium and rate data for the sulfation of several alcohols are summarized in Table II.

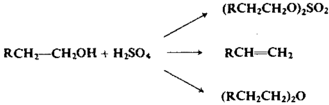
Note that *t*-butyl sulfate is not included in Table II because there is not sufficient evidence for its existence in aqueous solutions. It may be formed in an anhydrous system but may rapidly hydrolyze in water [2].

TABLE II. EQUILIBRIUM AND RATE CONSTANTS FOR THE SULFATION OF ALCOHOLS WITH EQUIMOLAR SULFURIC ACID AT 25 ± 0.1°C

| Alcohol | Ratio of[a] initial moles $H_2O/H_2SO_4$ | $K_{eq.}$[b] | Equivalent[c] concentration of aqueous $H_2SO_4$ | Estimated[c] $H_0$ | $k_2 \times 10^7$[d] |
|---|---|---|---|---|---|
| 2-Butanol | 0.194 | 0.61 | 82.0 | −7.15 | 147 |
| 2-Butanol | 0.250 | — | 81.8 | −7.10 | (180)[e] |
| 2-Butanol | 0.594 | 0.49 | 77.4 | −6.41 | 44 |
| 2-Butanol | 0.860 | — | 74.9 | −6.10 | (23)[e] |
| 2-Butanol | 1.290 | 0.50[f] | 70.4 | −5.55 | 8.0 |
| 2-Butanol | 2.175 | 0.29 | 63.2 | −4.70 | 1.4 |
| 2-Butanol | 3.980 | —[g] | 52.2 | −3.20 | 0.2 |
| 1-Butanol | 0.194 | 2.5[h] | 82.0 | −7.15 | 463 |
| Neopentyl | 0.194 | 5.2[i] | 82.0 | −7.15 | 367 |
| Methanol | 1.290 | 2.3 | 70.4 | −5.55 | 69 |
| Ethanol | 1.290 | 1.7 | 70.4 | −5.55 | 30 |
| 1-Butanol | 1.290 | 1.9 | 70.4 | −5.55 | 20 |
| Isobutyl | 1.290 | 2.2 | 70.4 | −5.55 | 17 |
| Neopentyl | 1.290 | 1.7 | 70.4 | −5.55 | 16 |
| 2-Propanol | 1.290 | 0.54 | 70.4 | −5.55 | 8.2 |
| 2-Pentanol | 1.290 | 0.64 | 70.4 | −5.55 | 7.6 |
| 3-Pentanol | 1.290 | —[i] | 70.4 | −5.55 | 6.7 |
| Pinacolyl | 1.290 | —[j] | 70.4 | −5.55 | 3.2 |
| Cyclohexanol | 1.290 | 0.70 | 70.4 | −5.55 | 11 |
| Methanol | 2.175 | 2.0 | 63.2 | −4.70 | 13 |
| 1-Butanol | 2.175 | 1.7 | 63.2 | −4.70 | 4.2 |
| Neopentyl | 2.175 | 1.3 | 63.2 | −4.70 | 4.0 |
| Methanol | 3.980 | 1.3 | 52.2 | −3.20 | 0.92 |

[a] The initial moles of alcohol and sulfuric acid were equal. [b] $K_{eq.}$ was calculated from the relation $K_{eq.} = (ROSO_3H)(H_2O)/(ROH)(H_2SO_4)$ and data taken after equilibrium had been attained. [c] The equivalent percent sulfuric acid was calculated by assuming that the added moles of alcohol were moles of water. Further assuming that a mole of alcohol will have an effect on lowering the acidity equal to that produced by a mole of water, we can obtain an approximate value by $H_0$ for these solutions from the tables of L. P. Hammett *et al.* [*J. Amer. Chem. Soc.* **54**, 2721 (1932); **56**, 827 (1934)]. It should be emphasized that these estimated values of $H_0$ are only approximate and do not necessarily remain constant during the reaction. [d] The dimensions of the rate constant are $(\text{seconds})^{-1}$ $(\text{mole per thousand grams of solution})^{-1}$. The precision = a unit in the second significant figure. [e] These values are calculated from the total rate of racemization data of R. L. Burwell as explained in the discussion section. [f] R. F. Robey [*Ind. Eng. Chem.* **33**, 1076 (1941)] has studied this equilibrium, and shown that it can be attained starting with either the alcohol or olefin. [g] The rate was too slow to estimate $K_{eq.}$. [h] C. M. Suter and E. Oberg [*J. Amer. Chem. Soc.* **56**, 677 (1934)] obtained a value of 2.69. [i] This value is only approximate since crystals appeared before equilibrium was completely attained. These crystals had been reported by F. C. Whitmore and H. S. Rothrock [*J. Amer. Chem. Soc.* **54**, 3431 (1932)] and are presumably neopentyl acid sulfate. [j] Hydrocarbon formation prevented attainment of equilibrium. [Reprinted from N. C. Deno and M. S. Newman, *J. Amer. Chem. Soc.* **72**, 3852 (1950). Copyright 1950 by the American Chemical Society. Reprinted by permission of the copyright owner.]

Several side reactions sometimes occur during the sulfation of alcohols, and they are shown in Eq. 2 [6a–c].



(2)

The use of stoichiometric amounts of acid gives low yields, 40–60%, but the use of twice the stoichiometric amount shifts the equilibrium so that 80–90% sulfated product is obtained (Eq. 3), as in the case of 1-tetradecanol [7]. The use of 20% fuming sulfuric acid also helps to shift the equilibrium toward sulfation by removal of water. Lauryl alcohol also gives improved yields by use of 20% fuming sulfuric acid [8a,b] (see also Table I). Other methods used to shift the equilibrium involve the azeotropic removal of water with carbon tetrachloride [9] or boron sulfate [10].

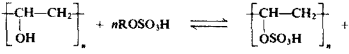
$$ROH + H_2SO_4 \rightleftharpoons ROSO_3H + H_2O \quad (3)$$

Sodium lauryl sulfate is prepared industrially in one process that involves the continuous "flash" process utilizing 170% of theory of 99% $H_2SO_4$. The reaction time is 60 sec at 60–70°C, and the reaction mixture is quickly neutralized, affording 85–95% product and 10–15% of unreacted alcohol [11].

Sulfuric acid has also been used to sulfate polyhydric alcohols. For example, glycerol gives a trisulfate with oleum, but only the disulfate with $SO_3$ vapor [12] or sulfuric acid [13]. Polyvinyl alcohol is sulfated with a mixture of $H_2SO_4$ and ethanol, to give an ethanol-soluble sulfated product. Omission of the ethanol gives either no reaction or a cross-linked polymer [14a,b].

The use of ethanol in the latter case may first give ethyl sulfate, which then may undergo sulfate interchange with polyvinyl alcohol (Eqs. 4, 5).

$$ROH + H_2SO_4 \rightleftharpoons ROSO_3H + H_2O \quad (4)$$



$$\left[\begin{array}{l}CH—CH_2\\ |\\ OH\end{array}\right]_n + nROSO_3H \rightleftharpoons \left[\begin{array}{l}CH—CH_2\\ |\\ OSO_3H\end{array}\right]_n + nROH \quad (5)$$

Further definitive studies are required to clarify the mechanism of this reaction. A similar process may take place when cellulose is sulfated with sulfuric acid using $C_3$ or higher alcohols (Eq. 6) [15a–e]. Apparently, the structure of the alcohol is critical because polyvinyl alcohol cannot be sulfated with $H_2SO_4$ and methanol. Furthermore, cellulose cannot be sulfated with $H_2SO_4$ and ethanol.

$$\text{Cell-OH} + \text{ROSO}_3\text{H} \rightleftharpoons \text{Cell-OSO}_3\text{H} + \text{ROH} \tag{6}$$

Cellulose can also be sulfated with $H_2SO_4$ at 5°C using methylene chloride or liquid $SO_2$ as a solvent.

Sugars can also be sulfated, and these are of interest as anticoagulants [16]. Polyethylene glycol ethers and esters are also sulfated using sulfuric acid and carbon tetrachloride at 35°C [17]. Ethylene and propylene glycols are sulfated without a solvent at 40°C, to give the monosulfates [18]. Bis(2-hydroxyethyl) sulfone gives the disulfate on sulfation with 60% oleum at 10°C in chloroform solvent [19a].

An examination of the recent patent literature indicates numerous references using concentrated sulfuric acid at room or elevated temperatures that is used to sulfate (from sulfate esters) alcohols and polyols [19b,c].

Secondary alcohols with polyether groups have been sulfated to produce surfactants under similar conditions [19d,e].

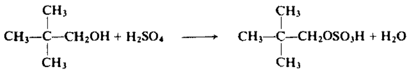
The kinetics and equilibrium data for the alcohol sulfation process (also with various different types of alcohols) using unconcentrated sulfuric acid has recently been published [19f].

### *2-1. Preparation of Sodium Lauryl Sulfate Using Fuming Sulphuric Acid* [20]

$$n\text{-C}_{12}\text{H}_{25}\text{OH} + \text{H}_2\text{SO}_4 \xrightarrow{-\text{H}_2\text{O}} n\text{-C}_{12}\text{H}_{25}\text{OSO}_3\text{H} \xrightarrow[-\text{H}_2\text{O}]{\text{NaOH}} n\text{-C}_{12}\text{H}_{25}\text{OSO}_3\text{Na} \tag{7}$$

To a 500-ml, three-necked flask equipped with a stirrer, dropping funnel, and drying tube is added 18.6 gm (0.1 mole) of lauryl alcohol dissolved in 100 ml of dioxane. The contents are cooled to 10–15°C and 12.2 gm (0.13 mole) of 20% fuming sulfuric acid is added. The mixture is stirred for $\frac{1}{2}$ hr at 10–15°C, neutralized with cold 10% sodium hydroxide, and concentrated under reduced pressure to afford 26.0 gm (91%) of product.

### *2-2. Preparation of Neopentyl Sulfate* [21]



$$\text{CH}_3\text{—}\overset{\overset{\text{CH}_3}{|}}{\underset{\underset{\text{CH}_3}{|}}{\text{C}}}\text{—CH}_2\text{OH} + \text{H}_2\text{SO}_4 \longrightarrow \text{CH}_3\text{—}\overset{\overset{\text{CH}_3}{|}}{\underset{\underset{\text{CH}_3}{|}}{\text{C}}}\text{—CH}_2\text{OSO}_3\text{H} + \text{H}_2\text{O} \tag{8}$$

To a cooled flask containing 15.6 gm (0.2 mole) of neopentyl alcohol is added dropwise 20 gm (0.2 mole) of conc. sulfuric acid. The reaction turns red-brown and is warmed up to room temperature. After 48 hr, the reaction mixture solidifies on cooling at 0°C. The crystals melt on warming to room temperature, and an infrared (IR) spectrum and VPC indicate complete conversion to the sulfate ester. Major IR absorption bands ($\mu$) are 3.40, 3.50 ($CH_3$); 6.75, 7.30 ($CH_2$); 8.0, 8.25, 8.30, 8.60 ($R\text{-}SO_3$); 9.45, 10.30, and 11.73.

### *2-3. Preparation of Sodium Ethoxylated Tridecyl Sulfate* [22]

$$RO(CH_2CH_2O)_4H \xrightarrow[2.\ NaOH]{1.\ H_2SO_4} RO(CH_2CH_2O)_4SO_3Na \qquad (9)$$

ROH derived from mainly tetramethylnonanol

To a three-necked flask equipped with a thermometer, drying tube, mechanical stirrer, and dropping funnel is added 375 gm (1.0 mole) of ethoxylated tridecyl alcohol.* The contents are cooled to 15°C, and then 282 gm (3.0 moles) of 20% oleum is added dropwise at such a rate as to maintain the temperature of the reaction at 15–20°C (about 30–45 min). The reaction mixture is stirred for 15 min and then poured simultaneously with a 30% sodium hydroxide solution into 400–500 ml of cold water to obtain pH 7.1–7.5. Then enough isopropyl alcohol (100–200 ml) is added to just form a solution. One gram of sodium carbonate is added as a buffer, and on standing, the final mixture separates into two layers. Sodium sulfate is added to just saturate the lower layer, and this layer is discarded. The product is obtained by concentration of the upper layer under reduced pressure to afford 449 gm (94%) of a gel-like product.

## B. Sulfur Trioxide

Sodium alkyl sulfates may be prepared as shown in Eq. 10.

$$ROH + SO_3 \longrightarrow ROSO_3H \xrightarrow[-H_2O]{NaOH} ROSO_3Na \qquad (10)$$

The reaction of methanol with sulfur trioxide vapor [23] or liquid [24] in carbon tetrachloride affords dimethyl sulfate as shown in Eq. 11.

$$2CH_3OH + 2SO_3 \longrightarrow 2CH_3OSO_3H \longrightarrow (CH_3O)_2SO_2 + H_2SO_4 \qquad (11)$$

The use of ethanol in liquid sulfur dioxide affords 74–86% of the acid sulfate, some disulfate, and sulfuric acid [25]. Excess sulfur trioxide affords ethionic acid (Eq. 12).

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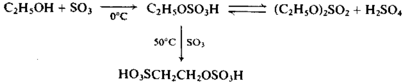
* One mole of tridecyl alcohol is reacted with 4.0 moles of ethylene oxide in the presence of $BF_3$ to give this starting material.



$$\begin{array}{c} C_2H_5OH + SO_3 \xrightarrow[0^\circ C]{} C_2H_5OSO_3H \rightleftharpoons (C_2H_5O)_2SO_2 + H_2SO_4 \\ {\scriptstyle 50^\circ C} \downarrow {\scriptstyle SO_3} \\ HO_3SCH_2CH_2OSO_3H \end{array} \tag{12}$$

A laboratory study [26] has reported that $SO_3$ vapor and $SO_3$ in liquid $SO_2$ are superior to other sulfating methods for converting 1-dodecanol and tetra-decanol into the sodium alkyl sulfates. The reaction of $SO_3$ vapor diluted with air with primary straight-chain alcohols derived from coconut oil (octyl, decyl, and lauryl) [27] and with primary branched-chain $C_{10}$ and $C_{13}$ alcohols prepared by the OXO process [22, 27] at 30–40°C gives good results in the laboratory-scale sulfation process. Solid alcohols such as cetyl and octadecyl are sulfated at 70–80°C or at lower temperatures in the presence of a solvent ($SO_2$, [28a,b] or tetrachloroethylene [29a]).

Secondary alcohols are also sulfated with $SO_3$ and air mixtures [29b]. Diols and triols are also sulfated with $SO_3$ vapor or with $SO_3$ in liquid $SO_2$

TABLE III

SULFATION OF GLYCOLS, TRIOLS, AND POLYETHER ALCOHOLS WITH $SO_3$

| Alcohol | Reagent[a] | Solvent | Temp. (°C) | Degree of sulfation | Ref. |
|---|---|---|---|---|---|
| Ethylene glycol | $SO_3$ | $SO_2$ | 50 | Di | *b* |
| Polyethylene glycol | $SO_3$ | $SO_2$ | — | Partial | *c* |
| Glycerol | $SO_3$ vapor | — | 40 | Di | *d* |
| Lauric monoglyceride | $SO_3$ | $SO_2$ | — | Mono | *b* |
| Tridecyl alcohol | $SO_3$ | — | 25 | Mono | *e* |
| Ethoxylated tridecyl alcohol (4 moles ethylene oxide) | $SO_3$ | — | 25 | Mono | *e* |
| Ethoxylated lauryl alcohol (3 moles ethylene oxide) | $SO_3$ | — | — | Mono | *f* |
| Ethoxylated dodecyl phenol (6 moles ethylene oxide) | $SO_3$ | — | — | Mono | *g* |

[a] 1.1 mole of $SO_3$ used per mole of alcohol. [b] F. G. Bordwell, R. D. Chapman, and C. E. Osborne, *J. Amer. Chem. Soc.* **81**, 2002 (1959). [c] E. W. Gluesenkamp, U.S. Patent 2,498,618 (1950). [d] F. W. Gray, U.S. Patent 2,868,812 (1959). [e] Enjay Chem. Co., Sulfation Procedures for Tridecyl Alcohol and Ethoxylated Tridecyl Alcohol. Technical Bulletin C-21, New York (1960); M. Kosmin, British Pat. 757,937 (1956); Atlas Powder Co., British Pat. 766,706 (1957). [f] E. E. Gilbert and B. Veldhuis, *J. Amer. Oil Chem. Soc.* **36**, 208 (1959). [g] E. E. Gilbert and B. Veldhuis, *J. Amer. Oil Chem. Soc.* **37**, 298 (1960).

[12]. Glycerol gives only the disulfate on reaction with $SO_3$, but the trisulfate on reaction with oleum [12].

Polyoxyethylene alcohols [30a,b] and alkylated phenols [31a,b] also react with $SO_3$-air vapor to give sulfates useful as commercial surface-active agents. Some ring sulfonation also takes place in the case of the alkylphenols. Sulfur trioxide in sulfuric acid, or oleum (30%) in the presence of benzoic acid, is reported to be useful for sulfonation of triethoxylated tallow alcohol. The benzoic acid is used to reduce the viscosity of the mixture [30c].

Carbohydrates can also be sulfated by $SO_3$ (in $CS_2$) to give water-soluble sulfates [32].

Some typical examples illustrating these results are shown in Table III.

The only disadvantage of the $SO_3$ method is that the products are usually somewhat darker in color. Lauryl alcohol may be sulfated with sulfur trioxide vapor diluted with nitrogen in the absence of solvents [27], as described in Preparation 2-4.

The use of small amounts of borohydride is reported to lead to light colored products [27c].

### *2-4. Preparation of Sodium Lauryl Sulfate* [20, 27, 33]

$$C_{12}H_{25}OH + SO_3 \longrightarrow C_{12}H_{25}OSO_3H \xrightarrow{NaOH} C_{12}H_{25}OSO_3Na \qquad (13)$$

**CAUTION:** This reaction should be carried out in a well-ventilated hood. Read the discussion of the properties and recommended safe-handling procedure for $SO_3$ in the following section before attempting to carry out this preparation.

A series of three flasks are connected (see Note a) to each other as follows: The first consists of an $SO_3$ evaporator, which consists of a 500 ml, three-necked flask with glass connections for a nitrogen inlet, thermometer, and exit tube for the $SO_3—N_2$ mixture. This flask is then connected to an empty safety flask, and this is then connected to a 500 ml three-necked reaction flask equipped with a glass mechanical stirrer and outlet tube for exiting nitrogen.

To the evaporator is added 49 gm (0.55 mole) of stabilized sulfur trioxide, and to the reaction flask is added 93 gm (0.5 mole) of *n*-lauryl alcohol. The evaporator is warmed, and while stirring vigorously, the temperature of the lauryl alcohol–$SO_3$ reaction is kept at 25°C but no higher than 30–35°C. The reaction mixture becomes a very dark brown during the first $\frac{1}{2}$ hr and the reaction is complete after $2\frac{1}{2}$ hr. Simultaneously, the reaction mixture and 200 ml of 10% sodium hydroxide (0.5 mole) are poured onto crushed icewater. A thick brown paste forms, which is then added to 2 l of cold methanol to precipitate the product. Filtration and drying afforded 107 gm (74%) (see Note b) of product. An infrared spectrum indicates the product contains less than 1–2% sodium sulfate.

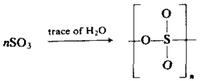
NOTES: (a) The flask fittings should be well secured, or else $SO_3$ will be lost. (b) During the early stages of the reaction, it appears that some of the $SO_3$ is passed through without reacting.

### a. THE PROPERTIES AND SAFE HANDLING OF SULFUR TRIOXIDE

Sulfur trioxide vapor is probably mostly monomeric. Freshly distilled $SO_3$ is a clear water-white liquid having the following properties [34–36]:

| | |
|---|---|
| B.p. | 44.8°C |
| M.p. | 16.8°C |
| $d_4^{20}$ | 1.9224 |
| Sp. heat | 0.77 cal/gm at 25°–35°C |
| Heat of dilution | 504 cal/gm |
| Heat of vaporization | 127.4 cal/gm |
| Viscosity | 1.590 centipoises at 30°C |
| Critical pressure | 83.8 atm |
| Critical density | 0.633 gm/ml |
| Critical temperature | 218.3°C |

When freshly distilled sulfur trioxide is exposed to traces of water vapor, it polymerizes to a solid with various degrees of cross-linking (Eq. 14).



$$n\mathrm{SO_3} \xrightarrow{\text{trace of } \mathrm{H_2O}} \left[ -\mathrm{O}-\overset{\overset{\displaystyle \mathrm{O}}{|}}{\underset{\underset{\displaystyle \mathrm{O}}{|}}{\mathrm{S}}}- \right]_n \qquad (14)$$

Thus far, this solid has found no commercial or practical value. Liquid sulfur trioxide can be stabilized against polymerization by the addition of small amounts of additives derived from boron, phosphorus, or sulfur.

Solid sulfur trioxide can exist in three forms. Stabilizers are added which will maintain cooled sulfur trioxide in the low melting $\gamma$- and $\beta$-forms. On warming to 35–40°C, the solids melt. The properties of the various solid sulfur trioxide forms are shown in Table IV [36].

Polymerization to the higher-melting $\beta$ and $\alpha$ forms is catalyzed at low temperatures by traces of moisture. To avoid this, it is recommended that the moisture content be below 0.3%.

TABLE IV

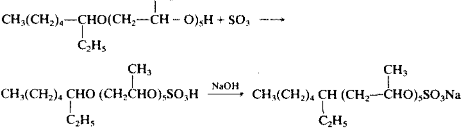
PHYSICAL PROPERTIES OF THE VARIOUS SOLID FORMS OF $SO_3$ [36]

| Solid $SO_3$ form: | $\alpha$ | $\beta$ | $\gamma$ |
|---|---|---|---|
| M.p. (°C) | 62.3 | 32.5 | 16.8 |
| $\Delta H$ (fusion) | 6200 | 2900 | 1800 |
| $\Delta H$ (sublimation) | 16,300 | 13,000 | 11,900 |
| Vapor pressure in Hg | | | |
| 0°C | 5.8 | 32 | 35 |
| 25°C | 73 | 344 | 433 |
| 75°C | 3000 | 3000 | 3000 |

Sulfur trioxide should be handled with the same precautions as any strong acid. In addition, because sulfur trioxide is a powerful oxidizing agent, contact with organic materials such as paper or sawdust may cause spontaneous combustion. Good ventilation or hoods should be used for chemical reactions. Rubber aprons and gloves should be worn, as well as safety glasses. Inhalation of fumes should be avoided, and in some cases, respiratory equipment may be needed. Only silicone- or Teflon-based greases should be used to lubricate glass joints.

Sulfur trioxide liquid should be stored at 33–38°C and at 40°C only if some solid matter is noted. Because sulfur trioxide boils at 44.8°C, storage containers should not be heated to this temperature. Storage containers should be made of glass or mild steel (not carbon steel). For further details, consult commercial product bulletins [35–37a].

### *2-5. Preparation of Sodium Sulfate Esters of Alkoxylated Alcohols* [37e]



$$CH_3(CH_2)_4-\underset{C_2H_5}{CHO}(CH_2-\overset{CH_3}{CH}-O)_5H + SO_3 \longrightarrow$$

$$CH_3(CH_2)_4\underset{C_2H_5}{CHO}\,(CH_2\overset{CH_3}{CHO})_5SO_3H \xrightarrow{NaOH} CH_3(CH_2)_4\underset{C_2H_5}{CH}\,(CH_2-\overset{CH_3}{CHO})_5SO_3Na \quad (14a)$$

*General Procedure.* Liquid sulfur trioxide diluted with an air stream is slowly added over a 2-hr period at 25°C to provide a conversion to the sulfate ester of the propoxylated polyol in methylene chloride as solvent. A low conversion prevents the formation of elimination products and unsaturation. At the end of the sulfation experiment, the temperature is increased to 35°C for 1 hr, and then air is bubbled through the solution. The product is neutralized with sodium hydroxide to pH 8–9, followed by extraction with petroleum ether to remove unreacted starting polyol. The surfactant from propylene oxide with 5 propylene oxide units had a surface tension (dynes/cm) of 31.9%.

## C. Chlorosulfonic Acid

Sulfation of alcohols with chlorosulfonic acid (Eq. 15) has been used in the laboratory and on an industrial scale to prepare sodium alkyl sulfates. The reaction is usually rapid in the presence or absence of solvents at 25–30°C and gives a product with little color. Unreactive solvents such as ether, dioxane, and halogenated hydrocarbons are commonly used in the sulfation reaction. Acetic acid has also been reported as a solvent for the sulfation of $C_5$–$C_{19}$ long-chain secondary alcohols. Table V gives several examples of the type of alcohols sulfated with chlorosulfonic acid.

$$\mathrm{ROH + ClSO_3H \xrightarrow{-HCl} ROSO_3H \xrightarrow[-H_2O]{NaOH} ROSO_3Na} \tag{15}$$

Chlorosulfonic acid has the disadvantage that hydrogen chloride is *evolved oftentimes incompletely*, which later affords sodium chloride impurities in the neutrilized product. This latter problem has hindered the early development of a continuous large-scale process. However, some continuous processes have been reported [37b–d]. Operating under vacuum or purging with nitrogen eliminates any residual hydrochloric acid. A batch process has been reported wherein one drum of chlorosulfonic acid is used per run [38].

### ***2-6. Preparation of Sodium Tridecyl Sulfate*** [22]

$$\mathrm{ROH + ClSO_3H \xrightarrow{-HCl} ROSO_3H \xrightarrow[-H_2O]{NaOH} ROSO_3Na} \tag{16}$$

R = tridecyl = isomeric mixture of branched-chain alcohols
with the major constituent being
tetramethylnonanols

To a three-necked flask equipped with a stirrer, dropping funnel, condenser, and drying tube, and containing 200 gm (1.0 mole) of tridecyl alcohol, is added dropwise 116.5 gm (1.0 mole) of chlorosulfonic acid at such a rate that the temperature does not exceed 25°C. After the addition, a nitrogen stream is passed through the reaction mixture to purge it of any remaining hydrogen chloride. The product is neutralized and worked up as in Preparation 2-3 to give 293 gm (97%) of product.

TABLE V. SULFATION OF ALCOHOLS USING CHLOROSULFONIC ACID

| Alcohol | Mole ratio of $ClSO_3H/ROH$ | Solvent | Reaction cond. Temp. (°C) | Time (hr) | Yield (%) | Ref. |
|---|---|---|---|---|---|---|
| Dodecyl | 1.0 | — | 25–30 | — | 90–100 | *a, b* |
| $C_{12}$, $C_{14}$, $C_{16}$, or $C_{18}$ | 1.08 | $CHCl_3$ | 25–30 | — | 65–75 | *c* |
| Tridecyl | 1.1 | — | 30–40 | ½–1 | 97 | *d* |
| Tridecyl–ethylene oxide adduct (1:4 mole ratio) | 1.0 | — | 20–25 | ½–1 | 93 | *d* |
| Coconut alcohols | — | — | 30 | — | — | *e* |
| Octadecyl, oleyl | — | $CCl_4$ | 25 | — | — | *e* |
| $C_{7-8}$ (OXO) | — | — | — | — | — | *f* |
| $C_{14}$ (OXO) | — | Ether | — | — | — | *g* |
| Polyesters of adipic acid with glycols | — | Ether | — | — | — | *h* |
| 2-(2,4-Dichlorophenoxy) ethanol | — | Ether | — | — | — | *i* |
| Lauric isopropanol amide | — | $CHCl_3$ | — | — | — | *j* |
| Fatty acid monoethanol amides | — | $CHCl_3$ | — | — | — | *k* |
| $C_{11}$–$C_{19}$ sec alc. or $C_{10,12,14,16}$ pri. alc. | 1.03 | $CH_3COOH$ | 0–5 | ½ | 80–95 | *l* |
| Sec. alcohols $C_8$–$C_{28}$ | — | Ether | −50 | — | — | *m* |
| Bis(hydroxyethyl)-methylamine | — | — | — | — | — | *n* |
| Chlorinated $C_{18}$ | — | $CHCl_3$ | — | — | — | *o* |
| Ethanolamines | — | $CHCl_3$ | 20–30 | — | — | *p* |
| Glycerol diether | — | Ether | 0 | — | — | *q* |
| Long-chain primary nitro | — | Ether | 20 | — | — | *r* |
| Hydroxyethylthio-succinate ester | — | $CCl_4$<br>(Ester group remains intact) | −5 | — | — | *s* |

[a] D. E. Gushee and O. L. Scherr, *Ind. Eng. Chem.* **51**, 798 (1959); P. Desnuelle and O. Micaelli, *Bull. Soc. Chim. France* **17**, 671 (1950); Henkel & Cie G.m.b.H., German Pat. 1,058,984 (1959). [b] Authors Laboratory (S.R.S.). [c] E. W. Maurer, A. J. Stirton, and J. K. Weil, *J. Amer. Oil Chem. Soc.* 37, 34 (1960). [d] Enjay Chem. Co. Tech. Bull. C-21 (1960). [e] J. K. Gunther, U.S. Dept. Commerce, OTS Rep. PB 35081, Frames 250–260 of FIAT Microfilm Reel C36 PB 12272 (1932); P. Sosis and L. J. Dringoli, *J. Amer. Oil Chem.* 47, 229 (1970). [f] I. G. Farbenindustrie A.-G., U.S. Dept. of Commerce, OTS Rep. PB 61127 Frames 854–857 of PB 25604 (1944). [g] T. H. van Bavel, H. Hoog, and P. W. O. Winga, Dutch Pat. 67,931 (1951). [h] F. Hölscher, German Pat. 803,835 (1951). [i] J. A. Lambrech, U.S. Pat. 2,573,769 (1951). [j] P. Desnuelle and O. Micaelli, *Bull. Soc. Chim. France* **17**, 671 (1950). [k] C. Paquot, *J. Rec. Centre Nat. Rec. Sci., Labs. Bellevue* (*Paris*) 169 (1950). [l] E. E. Dreger, G. I. Keim, G. D. Miles, L. Shedlovsky, and J. Ross, *Ind. Eng. Chem.* 36, 610 (1944). [m] R. A. G. Carrington and H. C. Evans, *J. Chem. Soc.* 1701 (1957). [n] M. Ishidate, Y. Sakarai, and S. Owari, *Pharm. Bull.* (*Tokyo*) **5**, 203 (1957). [o] J. K. Weil, A. J. Stirton, and E. W. Maurer, *J. Amer. Oil. Chem. Soc.* **32**, 148 (1955). [p] R. D. Stayner and R. A. Stayner, U.S. Pat. 2,697,657 (1954). [q] Farbwerke Hoechst A.-G., German Pat. 917,602 (1954). [r] Dehydag Deutsche Hydrierwerke G.m.b.H., German Pat. 881,509 (1953). [s] E. S. Blake, U.S. Pat. 2,630,449 (1953).

### *2-7. Preparation of Sodium Lauryl Sulfate* [20, 39]

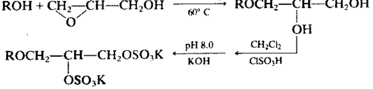
$$n\text{-}C_{12}H_{25}OH + ClSO_3H \xrightarrow{-HCl} n\text{-}C_{12}H_{25}OSO_3H \xrightarrow[-H_2O]{NaOH} n\text{-}C_{12}H_{25}OSO_3Na \quad (17)$$

To a flask equipped as in Preparation 2-5 and containing 250 gm (1.35 mole) of lauryl alcohol is added dropwise 156 gm (1.35 mole) of chlorosulfonic acid, keeping the temperature at about 25°C but not higher than 30°C. Nitrogen is passed through the reaction mixture to purge it of any remaining hydrogen chloride. The reaction mixture and 10% sodium hydroxide solution are simultaneously poured with good stirring into 1000 gm of cold water–crushed ice to give pH 7.7–8.0. The reaction mixture is worked up as in Preparation 2-3 to give 259 gm (90%) of product.

### *2-8. General Procedure for the Preparation of the Sulfate Derivative of a Polyoxyalkylene Oligomer* [37e, f]

To a flask equipped with a mechanical stirrer, a dropping funnel, a condenser, a thermometer and a nitrogen inlet–outlet was added a solution of polyoxyalkylated oligomer in methylene chloride (50/50). Then a slight excess of chlorosulfonic acid diluted with methylene chloride (50/50) was added dropwise over a 2-hr period while keeping the temperature at 10–25°C using an ice bath and nitrogen flow (2–51/min) to remove hydrogen chloride from the reaction zone. After the addition was complete, the mixture is allowed to stir for 12 hr at 35–40°C and then the methylene chloride removed on a rotary evaporator under reduced pressure. The product is neutralized with 50% sodium hydroxide to pH 7.5–9.0 and then cooled to 10°C. The precipitated sodium chloride and sodium sulfate are filtered and the product extracted with petroleum ether to remove unreacted polyoxyalkylene oligomer. When concentrated, the product shows anion surfactant properties. For additional examples, see Table VI.

It has been reported that $C_{10}$–$C_{20}$ linear alkyl alcohols can be reacted with glycidol to produce $C_{10}$–$C_{20}$ linear alkyl glycerol ethers. These can be sulfated by reaction with chlorosulfonic acid to produce useful biodegradable surfactants.



(18)

## TABLE VI

### SULFATION OF ALCOHOLS USING CHLOROSULFONIC ACID

|  | moles |  | Reaction Conditions |  |  |
|---|---|---|---|---|---|
| Alcohol | $ClSO_3H$ | Solvent | Temp.°C | Yield % | Ref. |
| 2-Ethylhexyl | — | — | 5–13 | — | *a* |
| $C_{10}$–$C_{17}$<br>Secondary Alcohols<br>1.0 | 1.05–1.07 | $\frac{CH_2Cl_2}{NaCl}$ | 0 | 90–97 | *b* |
| Bis(hydroxymethyl)<br>Phosphinic Acid<br>0.41 | 0.88 | $CHCl_3$<br>(500 ml) | 10–15 | 90<br>(As sodium salt) | *c* |
| Lauryl<br>1.69 | 1.60 | Conc. HCl<br>1.11 | 5 | —<br>(continuous process) | *d* |
| Ethoxylated–<br>Propoxylated<br>Secondary<br>Alcohols ($C_{14}$–$C_{18}$)<br>1.5 | 1.5–1.6 | — | 10–30 | — | *e* |

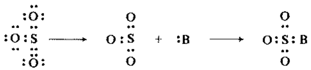
[a] Y. A. Smiraova and L. N. Nemtsova, USSR SU 1,133,265 (1985); *Chem. Abstr.* **103**, 5889b (1985). [b] J. B. Wilken, U.S. Pat. 3,647,851 (1972). [c] L. H. Chance, U.S. Pat. 3,494,720 (1970). [d] N. Whitman, U.S. Pat. 3,370,926 (1968) and U.S. Pat. 3,337,601 (1967). [e] H. Baumann, W. Umbach, and W. Stein, U.S. Pat. 3,931,271 (1976).

### *2-9. General Procedure for the Preparation of Sodium Alkyl Sulfates of Secondary Alcohols* [40]

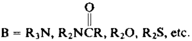
To 200 gm of anhydrous ether at 0–5°C, is added 116.5 gm (1.0 mole) of chlorosulfonic acid with stirring. Then 1.0 mole of a secondary alcohol dissolved in 400 gm of anhydrous ether is added dropwise while keeping the temperature at 0–5°C (10–15 min). The mixture is then purged with nitrogen until all the dissolved hydrogen chloride is removed (approx. 35 min). The mixture is then poured onto 80 gm of 50% (1.0 mole) sodium hydroxide in 300 gm of ice. Additional 50% sodium hydroxide is added to adjust the pH to 10. The mixture is then diluted with 800 ml of isopropanol and 500 ml of water and extracted with two 500-ml portions of petroleum ether; the alcohol–water layer is separated and concentrated under reduced pressure; and the residue is dried at 40°C in a vacuum oven to give the product.

## D. Sulfur Trioxide Complexes

Sulfur trioxide as a Lewis acid combines with Lewis bases to form coordination compounds or complexes as shown in Table VII [34] and Eq. 19.

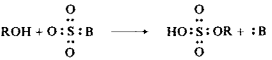


$$\overset{:\ddot{O}:}{\underset{:\ddot{O}:}{:\ddot{O}:S}} \longrightarrow \overset{O}{\underset{O}{O:\ddot{S}}} + :B \longrightarrow \overset{O}{\underset{O}{O:\ddot{S}:B}} \tag{19}$$



$B = R_3N, R_2N\overset{\overset{O}{\|}}{C}R, R_2O, R_2S$, etc.

The reactivity of the complex with alcohols (Eq. 20) varies inversely as the strength of the base used. Trimethyamine (p$K_a$, $H_2O$, 10.72) forms a



$$ROH + \overset{O}{\underset{O}{O:\ddot{S}:B}} \longrightarrow \overset{O}{\underset{O}{HO:\ddot{S}:OR}} + :B \tag{20}$$

stronger complex than pyridine (p$K_a$, $H_2O$, 5.22). These complexes are milder than free $SO_3$ as a sulfating agent and several examples are described in Table VII.

The trialkylamine $SO_3$ complexes are formed either by the reaction of $SO_3$ (liquid or vapor) or $ClSO_3H$ with the trialkylamine in the presence or absence of a solvent at low temperatures as described in Table VII. Dialkylamines, dioxane, thioxane, and amides also react by a similar process to form their respective $SO_3$ complexes of varying stability.

The pyridine–$SO_3$ complex is a white solid [41] soluble in less than 1% by weight in most organic solvents (pyridine, nitrobenzene, cyclohexane,

## TABLE VII

### Preparation of Sulfur Trioxide Complexes

| Reagent in solution | Reagent added dropwise or as a vapor | Solvent | Temp. (°C) | Yield (%) | Product | M.p. (°C) | Ref. |
|---|---|---|---|---|---|---|---|
| $SO_3$ | Pyridine | $CCl_4$ | 10–20 | — | $C_5H_5N:SO_3$ | 160–165 | *a* |
| $SO_3$ | Pyridine | $CHCl_3$ | — | 100 | $C_5H_5N:SO_3$ | | *b* |
| $SO_3$ | Pyridine in 1,2-dichloroethane | 1,2-Dichloroethane | 0 | 95 | $C_5H_5N:SO_3$ | | *c* |
| Pyridine | $SO_3$ liq. | $CHCl_3$ | — | — | | | *d* |
| Pyridine | $SO_3$ liq. | $SO_2$ | — | 97 | $C_5H_5N:SO_3$ | | *e* |
| Pyridine | $SO_3$ liq. | — | — | 87 | $C_5H_5N:SO_3$ | | *f* |
| Pyridine | $SO_3$ vapor | — | — | — | $C_5H_5N:SO_3$ | | *g* |
| Pyridine | $ClSO_3H$ | $CHCl_3$ | 0 | 62 | $C_5H_5N:SO_3$ | | *h* |
| $(CH_3)_3N$ | $SO_3$ vapor | — | — | — | $(CH_3)_3N:SO_3$ | 239 dec | *i* |
| $(CH_3)_3N$ | $SO_3$ vapor | $CHCl_3$ | — | — | $(CH_3)_3N:SO_3$ | | *j* |
| $(CH_3)_3N$ | $SO_3$ vapor | $SO_2$ | −10 | — | $(CH_3)_3N:SO_3$ | | *e* |
| $(CH_3)_3N$ | $SO_3$ liq. | $CHCl_3$ | 0–10 | — | $(CH_3)_3N:SO_3$ | | *d* |
| $(CH_3)_3N$ | $ClSO_3H$ | $ClC_6H_5$ | 10 | — | $(CH_3)_3N:SO_3$ | | *k* |
| $(C_2H_5)_3N$ | $SO_3$ vapor | — | — | — | $(C_2H_5)_3N:SO_3$ | 93 | *l* |
| $(C_2H_5)_3N$ | $SO_3$ liq. | $CCl_4$ | — | — | $(C_2H_5)_3N:SO_3$ | | *m* |
| $(C_2H_5)_3N$ | $ClSO_3H$ | $ClC_6H_5$ | 10 | — | $(C_2H_5)_3N:SO_3$ | | *n* |
| $(CH_3)_2NH$ | $SO_3$ vapor | — | — | — | $(CH_3)_2NHSO_3$ | 85–90 | *o* |
| $(CH_3)_2NH$ | $SO_3$ liq. | $SO_3$ | — | — | $(CH_3)_2NHSO_3$ | | *e* |
| $(CH_3)_2NH$ | $ClSO_3H$ | $CS_2$ | 0 | 62 | $(CH_3)_2NHSO_3$ | | *g* |
| $(CH_3)_2NH$ | $ClSO_3H$ | $CHCl_3$ | 0 | 62 | $(CH_3)_2NHSO_3$ | | *p* |
| 2-Methylpiperidine | $SO_3$ liq. | $CHCl_3$ | 10–20 | — | $CH_3C_5H_4NHSO_3$ | — | *q* |
| 2-Methylpiperidine | $ClSO_3H$ | — | <30 | — | $CH_3C_5H_4NHSO_3$ | — | *r* |
| Quinoline | $SO_3$ liq. | 1,2-Dichloroethane | — | — | Quinoline:$SO_3$ | — | *f* |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| DMF | $SO_3$ *liq.* | — | 0–5 | — | DMF:$SO_3$ | Not characterized | *s* |
| DMF | $SO_3$ vapor | — | 0–5 | — | DMF:$SO_3$ | | *t* |
| Bis(2-chloroethyl)-ether | $SO_3$ vapor | — | — | — | Bis(2-chloro-ethyl ether)$SO_3$ | — | *u* |
| Dioxane | $SO_3$ liq. | — | — | — | Dioxane:$SO_3$ | 75 dec | *v* |
| Dioxane | $SO_3$ liq. | 1,2-Dichloro-ethane | — | — | Dioxane:$SO_3$ | | *w* |
| Dioxane | $SO_3$ vapor | 1,2-Dichloro-ethane | — | — | Dioxane:$SO_3$ | | *x* |
| Dioxane | $ClSO_3H$ | 1,2-Dichloro-ethane | — | — | Dioxane:$SO_3$ | | *y* |
| Thioxane | $SO_3$ | $CCl_4$ | — | — | Thioxane:$SO_3$ | 124 | *z* |
| Thioxane | $ClSO_3H$ | $CCl_4$ | — | — | Thioxane:$SO_3$ | | *z* |
| Thioxane | $ClSO_3H$ | 1,2-Dichloro-ethane | — | — | Thioxane:$SO_3$ | | *z* |

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carbon tetrachloride, chloroform, dioxane, acetone ethyl ether) [42] except DMF [34]. It forms a 20% by weight solution in $SO_2$ at – 10°C [34]. The complex is also soluble in conc. $H_2SO_4$, HCl or $HClO_4$ and can be recovered unchanged by precipitation with cold water [43].

Two moles of sulfur trioxide can also form a complex (m.p. 83–85°C) [44] with pyridine, but the reports in this area have been few, and further research on this complex is necessary. The usefulness of this latter complex as a sulfonating agent for heterocyclic compounds has also been reported [44].

The trimethylamine–$SO_3$ complex is the most stable and is considerably more stable than the pyridine–$SO_3$ complex. The more basic amines give the more stable $SO_3$ complexes. At 50°C, a 25% by weight water solution of $(CH_3)_3N:SO_3$ is only 6.4% hydrolyzed in 24 hr [45]. Thus, the latter complex is useful for sulfation reaction in aqueous solution.

The main disadvantage of the use of all the amine–$SO_3$ complexes is that they leave an unpleasant odor of traces of the free amine in the product, which is somtimes difficult to remove. The use of $CHCl_3$ probably leads to isonitrile odors.

The triethylamine–$SO_3$ complex is more soluble in acetone and 1,2-dichloroethane than the trimethyl analog. However, the triethylamine complex is less stable but more reactive. It is recommended that this complex be stored under refrigeration prior to use [45].

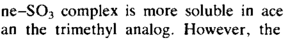
Sulfur trioxide–dioxane complex is unstable [46a–c] and difficult to isolate. The latter adduct is more reactive than the $SO_3$–pyridine complex and decomposes quickly on contact with water to give dioxane and sulfuric acid [46c].

The DMF–$SO_3$ adduct has not yet been isolated or fully characterized. However, solutions of it have been found to be useful in sulfating alcohols [47a–f].

$SO_3$ also reacts with other trialkylamines [48a–e], amides [47a,d, 49a–c], sulfides [47b, 50], and ethers [47b, 50], to give complexes with interesting solubility properties.

### *2-10. Preparation of Pyridine–$SO_3$ Complex*

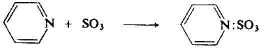
METHOD A. CHLOROSULFONIC ACID [20, 51]



(21)

To a flask containing 79 gm (1.0 mole) of pyridine dissolved in 500 ml of chloroform is added dropwise with stirring 116.5 gm (1.0 mole) of chlorosulfonic acid over a 1-hr period. The white solid is filtered, washed with dry chloroform, and dried to afford 192 gm (89%), m.p. 160–165°C.

METHOD B. SULFUR TRIOXIDE [20, 52]



(22)

To a cooled flask containing 98.8 gm (1.25 mole) of pyridine dissolved in 400gm of chloroform is added dropwise with stirring 80 gm (1.0 mole) of stabilized liquid sulfur trioxide. The resulting white precipitate is filtered, washed with chloroform, and dried under reduced pressure to afford 132 gm (83%), m.p. 165°C.

### *2-11. Preparation of Trimethylamine–$SO_3$ Complex* [20, 53]

$$(CH_3)_3N + SO_3 \longrightarrow (CH_3)_3N{:}SO_3 \qquad (23)$$

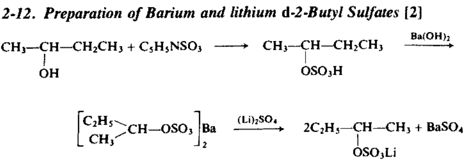
To a cooled flask containing 74 gm (1.0) mole of trimethylamine dissolved in 400 gm of chloroform is slowly added dropwise with stirring 80 gm (1.0 mole) of stabilized liquid sulfur trioxide. The white precipitate is filtered, washed with chloroform, and dried, to afford 101 gm (73%), m.p. 235–241°C (reported 239°C dec.). [54].

Sulfur trioxide complexes sulfate alcohols in good yields. Pyridine–$SO_3$ complexes sulfate ethanol [52], 2-butanol [2], benzyl alcohol [53], primary and tertiary alcohol derivatives of 1,4-naphthoquinone [54], alcohols from oxidized petroleum fractions have also been sulfated on a semicommercial scale at 50–95°C in 30 min [55]. Sterols [56a–c], carbohydrates [57a–c], and polyols [58] are also sulfated with pyridine–$SO_3$. Trimethylamine–sulfur trioxide behaves in a similar fashion and has been used to sulfate 1- and 2-propanol [59], phenols, and glycols [60a–c]. It is interesting to note that 1- and 2-propanol may be separated by selectively sulfating 1-propanol by $(CH_3)_3NSO_3$ in chloroform at room temperature [59]. Elevated temperature causes sulfation of 2-propanol [59].

Dioxane–Sulfur trioxide quantitatively sulfates many alcohols [61a–c].

Several examples of the sulfation with $SO_3$ complexes are described in Table VIII.

### *2-12. Preparation of Barium and lithium* d*-2-Butyl Sulfates* [2]



$$CH_3-\underset{OH}{CH}-CH_2CH_3 + C_5H_5NSO_3 \longrightarrow CH_3-\underset{OSO_3H}{CH}-CH_2CH_3 \xrightarrow{Ba(OH)_2}$$

$$\left[\begin{matrix}C_2H_5\\CH_3\end{matrix}\!\!>CH-OSO_3\right]_2 Ba \xrightarrow{(Li)_2SO_4} 2C_2H_5-\underset{OSO_3Li}{CH}-CH_3 + BaSO_4$$

(24)

TABLE VIII

Sulfation of Alcohols with $SO_3$ Complexes

| Alcohol | $SO_3$ complex | Solvent | Temp. (°C) | Yield (%) | Ref. |
|---|---|---|---|---|---|
| (+) 2-Butyl | $SO_3$–pyridine | $C_6H_6$ | 80 | 90 | *a* |
| *d*-2-Butyl | $SO_3$–dioxane | — | 0 | — | *b* |
| Ethanol | $SO_3$–pyridine | — | 25 | — | *c* |
| Ethanol | $SO_3$–trimethylphosphine oxide | — | — | — | *d* |
| 1-Propanol | $(CH_3)_3N:SO_3$ | $CHCl_3$ | 25 | — | *e* |
| 2-Propanol | $(CH_3)_3N:SO_3$ | — | 125 | — | *e* |
| *d*- and *dl*-Pinacolyl | $SO_3$–pyridine | — | 125 | — | *f* |
| Propargyl | $SO_3$–pyridine | $CCl_4$ | 0–25 | — | *g* |
| Hydroxylated polybutadienes | $SO_3$–pyridine | — | 90 | — | *h* |
| Polyethylene and propylene glycols | $SO_3$–amine | — | 100 | — | *i* |
| Hexoses | $SO_3$–pyridine | — | — | — | *j* |
| Cyclohexa- and Cyclohepta-amyloses | $SO_3$–pyridine | — | 85 | — | *k* |
| Cellulose | $SO_3$–pyridine | — | — | — | *l* |
| Cellulose | $SO_3$–dichloroethyl ether | $CHCl_3$ | — | — | *m* |
| Starch | $SO_3$–$R_3N$ | $H_2O$ | 25 | — | *n* |
| Hydroxyethyl- | $SO_3$–methylpyridine | — | 190 | — | *o* |
| (−)Borneol | $SO_3$–dioxane | $(\text{-}CH_2Cl)_2$ | 0–10 | 79 | *p* |

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To a flask containing 8.2 gm (0.11 mole) of *d*-2-butanol ($[\alpha]_D^{25}$ + 11.30) is added 0.5 ml of pyridine and 16.4 gm (0.104 mole) of pyridine-sulfur trioxide. The mixture is stirred at 25°C for 20 min (see Note a), poured into 100 ml of water, and then excess aqueous barium hydroxide is added. The mixture is kept at 25°C for 40 min (see Note b), and then an excess of carbon dioxide is bubbled in to precipitate the excess barium hydroxide as barium carbonate. The mixture is filtered and the solution barium *d*-2-butyl sulfate ($[\alpha]$ + 10.53 ± 0.04) is treated with a stoichiometric amount of lithium sulfate solution. The precipitated barium sulfate is filtered and the solution concentrated under reduced pressure, to afford 5.63 gm (32%) of lithium *d*-2-butyl sulfate monohydrate.

NOTES: (a) Stirring for 1 hr gives a higher yield, but some racemization occurs. (b) The alkaline hydrolysis step is necessary to remove the bound pyridine.

For additional examples see Table IX.

### *2-13. Preparation of Sodium Lauryl Sulfate Using the Pyridine–SO$_3$ Complex* [20]

$$C_{12}H_{25}OH + C_5H_5N{:}SO_3 \longrightarrow C_{12}H_{25}OS\overset{-}{O}_3\underset{+}{\overset{H}{N}}C_5H_5 \xrightarrow{NaOH}$$

$$C_{12}H_{25}OSO_3Na + C_5H_5N + H_2O \quad (25)$$

To a flask equipped with a magnetic stirrer and containing 93 gm (0.5 mole) of lauryl alcohol dissolved in 100 gm of dioxane is added portionwise 97.5 gm (0.5 mole) of pyridine–sulfur trioxide. The reaction is stirred for 24 hr, at 30–40°C and then neutralized with 10% sodium hydroxide. The reaction is poured into cold methanol to precipitate the product. The filtered product is dried to afford 70 gm (50%) of product. The product retains some of the odor of pyridine, which is difficult to remove.

## E. Sulfamic Acid

Sulfamic acid is mainly used to sulfate alcohols susceptible to ring or chain sulfonation reactions. The reactions are usually carried out by heating for 2 hr at 125–140°C to give the ammonium sulfate, as shown in Eq. (26).

$$ROH + H_2NSO_3H \longrightarrow ROSO_3^{-}\overset{+}{N}H_4 \qquad (26)$$

Sulfamic acid has been effectively used to sulfate long-chain polyoxyethylated condensates [22], phenolic ethylene oxide condensates [62a,b],

## TABLE IX

### PREPARATION OF SULFATE ESTERS USING SULFUR TRIOXIDE COMPLEXES

| Alcohol | Sulfur Trioxide Complex | Solvent | Temp.°C. | Product | Yield % | Ref. |
|---|---|---|---|---|---|---|
| Decyl Alcohol | $SO_3$–Dioxane 2.5–3.5:1 | — | 0–5 | Na decyl sulfate | — | *a* |
| $Me_3COH_3$<br>3-Methyl-3-pentanol<br>or<br>$H_2NCH_2CMe_2OH$ | $SO_3$–Pyridine<br>or<br>$OS_3$–$Et_3N$<br>$SO_3$–$(CH_3)_3N$ | $Et_2O$<br>or<br>MeOH | 115–116 | — | 81 | *b* |
| Ethylene Glycol | $SO_3$–Triethyl phosphate | — | 35–40 | — | — | *c* |
| Ethylhydroxy Acetate | $SO_3$–Pyridine | Dioxane | — | — | — | *d* |
| Cellulose | $SO_3$–DMF |  | 27–35 | — | — | *e* |
| Benzyl Alcohol | $SO_3$–Dioxane | Dioxane | 10 | — | — | *f* |
| Aliphatic Alcohol | $SO_3$–$(CH_3)_3$3N | — | — | — | 71–80 | *g* |

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polyoxyethylated phenol-formaldehyde resins [63], and unsaturated alcohols olefinic and acetylenic [64a–e]).

Sulfamic acid sulfates secondary alcohols with great difficulty unless pyridine is added [65].

Primary alcohols are also sulfated in good yields with sulfamic acid in the presence of pyridine at 100°C in $\frac{1}{2}$–1 hr [5, 64c].

Other amines (γ-picoline) and amides (urea, thiourea, acetamide) are also effective catalysts, and urea was found to be the best [66]. Higher aliphatic alcohols are sulfated with sulfamic acid in the presence of $C_1$–$_4$ alcohols [67] or a polyethylene glycol ether containing 1–20 ethylene oxide units [68]. Sulfamic acid–urea is a very effective sulfation reagent for starch [69] and cellulose [70], and sulfation occurs at 140°C in $\frac{1}{2}$ hr. Several examples of the sulfation of various alcohols with sulfamic acid are shown in Table X.

### *2-14. Preparation of Ammonium Ethoxylated Tridecyl Sulfate* [22]

$$RO(CH_2CH_2O)_4H + H_2NSO_3H \xrightarrow[140°C]{N_2} RO(CH_2CH_2O)_4\overset{-}{S}O_3\overset{+}{N}H_4 \tag{27}$$

R = tridecyl (mostly tetramethylnonanols)

To a three-necked flask equipped with a mechanical stirrer, a thermometer, and a nitrogen inlet and outlet, and containing 367 gm (1.0 mole) of ethoxylated tridecyl alcohol* is added 102 gm (1.05 mole) of sulfamic acid. The reaction mixture is vigorously stirred and gradually heated to 140–150°C while maintaining a nitrogen flow over the contents. After 1 hr, the reaction mixture is cooled, a small amount of ammonium hydroxide added to neutralize the remaining sulfamic acid, and the product removed to afford 468 gm (99%).

### *2-15. Preparation of Ammonium Undecenyl Sulfate* [22b]

$$CH_2{=\!=}CH(CH_2)_9{-}OH + H_2NSO_3H + \text{Urea} \xrightarrow[110\text{–}120°C]{} CH_2{=\!=}CH(CH_2)_9{-}OSO_3^-\overset{+}{N}H_4 \tag{28}$$

To a three necked flask equipped with a mechanical stirrer, a thermometer, a condenser, and a nitrogen inlet and outlet, and containing 170.0 g (1.0 mole) of undecenyl alcohol is added 120 g (1.05 moles) of sulfamic acid and 3.0 gm (0.05 mole) of urea. The reaction mixture is vigorously stirred and heated under a nitrogen atmosphere to 110–120°C until the acid number remains constant and a sample forms a clear solution

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* See Preparation 2-3 for the description of the origin of this alcohol.

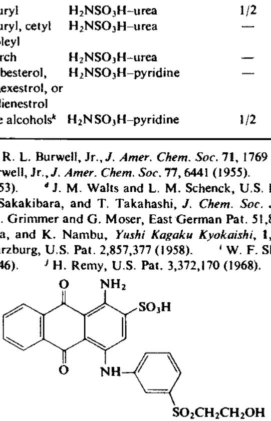
TABLE X

SULFATION OF ALCOHOLS WITH SULFAMIC ACID

| | | Reaction conditions | | | |
|---|---|---|---|---|---|
| Alcohol | Sulfating reagent | Time (hr) | Temp. (°C) | Yield sulfate ester (%) | Ref. |
| *s*-Butanol | $H_2NSO_3H$–pyridine | 1 | 90–100 | 60–70 | *a* |
| *s*-Butanol | $H_2NSO_3H$ | 2 | 100 | 22 | *a* |
| $C_3$–$C_6$ | $H_2NSO_3H$–pyridine | 1 | 100 | — | *b* |
| $C_{10}$–$C_{18}$ | $H_2N$–$SO_3H$–morpholine | 6 | 100–120 | — | *c* |
| sec $C_8$–$C_{25}$ | $H_2NSO_3H$ | 3 | 115–125 | — | *d* |
| Methyl ricinoleate | $H_2NSO_3H$ | 1 | 145 | — | *e* |
| Lauryl | $H_2NSO_3H$–urea | 1/2 | 125–135 | — | *f* |
| Lauryl, cetyl oleyl | $H_2NSO_3H$–urea | — | 125–145 | — | *g* |
| Starch | $H_2NSO_3H$–urea | — | — | — | *h* |
| Stilbesterol, hexestrol, or dienestrol | $H_2NSO_3H$–pyridine | — | — | — | *i* |
| Dye alcohols[k] | $H_2NSO_3H$–pyridine | 1/2 | 100 | 94 | *j* |

[a] R. L. Burwell, Jr., *J. Amer. Chem. Soc.* **71**, 1769 (1949). [b] G. M. Calhoun and R. L. Burwell, Jr., *J. Amer. Chem. Soc.* **77**, 6441 (1955). [c] R. F. Neighbors, U.S. Pat. 2,649,469 (1953). [d] J. M. Walts and L. M. Schenck, U.S. Pat. 3,395,170 (1968). [e] S. Komori, S. Sakakibara, and T. Takahashi, *J. Chem. Soc. Japan, Ind. Chem. Sec.* **57**, 83 (1954). [f] R. Grimmer and G. Moser, East German Pat. 51,853 (1966). [g] S. Komori, S. Sakakibara, and K. Nambu, *Yushi Kagaku Kyokaishi*, **1**, 73 (1952). [h] I. Martin and O. B. Wurzburg, U.S. Pat. 2,857,377 (1958). [i] W. F. Short and P. Oxley, British Pat. 577,666 (1946). [j] H. Remy, U.S. Pat. 3,372,170 (1968).

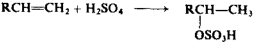
[k]



in water. To the reaction product is added 278 g of water and 17 g of 30% aqueous ammonium hydroxide. The solution is clear, reddish in color with a pH of 7.0, and contains 33.3% of active undecyl alcohol sulfate ammonium salt. The iodine value of the product is 62.3.

## 3. MISCELLANEOUS METHODS

(1) Sulfation of olefins such as ethylene, propylene, butylene, long-chain alkenes $C_8$—$C_{18}$, etc. [71a–g] (Eq. 29).



$$RCH{=}CH_2 + H_2SO_4 \longrightarrow \underset{\displaystyle OSO_3H}{RCH}{-}CH_3 \tag{29}$$

(2) Sulfation of hydroxamic acids [72].

(3) Sulfation of oximes and hydroxylamines [73a–d].

(4) Sulfation of unsaturated acids, esters, and amides [71d,g, 74a–d].

(5) Sulfation of ethers [75a–e].

(6) Sulfation of long-chain alcohols with diammonium imidodisulfonate,$NH(SO_3NH_4)_2$, at 140°C in dialkylamide solvents to give 61–80% yields of product [76a–c].

(7) Sulfation of long-chain hydroperoxides by means of sulfur dioxide [77].

(8) Sulfoxidation of alcohols with $SO_2$ and $O_2$ [78].

(9) Sulfation of alcohols by $SO_3$ interchange with naphthalenesulfonic acids [79].

(10) Sulfation of 9-hydroxyanthracene with $SO_3$–pyridine [80].

(11) Sulfation of *leuco* vat dyes [48d, 81a–h].

(12) Sulfation of phenols with potassium persulfate (Elbs sulfation) [82a–d].

(13) Sulfation of phenols with sulfamic acid [83a–e].

(14) Sulfation of phenols with $SO_3$–amine complexes [52, 84a–s].

(15) Sulfation of alkenes with chlorosulfonic [85a] and flurosulfonic [85b–e].

(16) Sulfation of alcohols with sulfuryl chloride [86a,b].

(17) Sulfation of haloalkanes with $SO_3$, $CISO_3H$ $FSO_3H$, $H_3SO_4$, or oleum [87a–i].

(18) Sulfation of alcohols by means of acetyl sulfate [88a,b].

(19) Sulfation of cellulose and starch with $SO_3/(CH_3)_2SO$ complex [89].

(20) Sulfation of hydroxylated polybutadienes [90].

(21) Sulfation of androsterone with L-ascorbic acid 3-sulfate [91].

(22) Sulfate transfer from ascorbic acid sulfate or 5,6-*O*-isopropylidene ascorbic acid sulfate under oxidative conditions to alcohols such as 1-octanol and 3β-cholestanol [92].

(23) Sulfation of alcohols with N-substituted sulfamic acids [93].

(24) Reaction of hydroperoxides with $SO_2$ to form sulfates [94].

(25) Preparation of primary sulfates by the simultaneous reaction of isobutylene with ethylene. Other branched-chain olefins can be used in place of isobutylene [95].

(26) Preparation of sodium alkyl sulfates by considering at 200–300°C a fatty acid and the sodium salt of 2-hydroxythylsulfuric acid [96].

(27) Preparation of monosulfate esters by the reaction of alcohols with sulfuric acid–dicyclohexylcarbodiimide in solvents such as dimethylformamide. The latter reagent is ineffective on phenols or oximes [97a–d].

(28) Sulfation of $C_8$–$C_{22}$ olefins [98–99].

(29) Preparation of perfluoroalkyl fluorosulfate by reacting hexafluoropropane with $SO_3$ in the presence of a catalyst [100].

(30) Reaction of fluoroalkyl iodies with $SO_3$ to give fluoroalkylsulfates [101].

(31) Sulfation of higher alkanols with $RSO_2$ Cl [102].

(32) Sulfation of lauryl alcohols with a mixture of $SO_3$ and $SO_2$ [103–104].

(33) Preparation of organic sulfates and sulfonates in a continuous thin-film reactor using $SO_3$-containing gases [165].

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# CHAPTER 4/SULFENIC ACIDS AND SULFENIC ACID DERIVATIVES

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## 1. INTRODUCTION

The sulfenic acids and their derivatives are compounds based on the structure RSX, where X = OH for the acids, and for the derivatives, X is any other (electronegative) nucleophilic group, such as F, Cl, Br, I, OR, $NR_2$, SCN, or OSR.

Few sulfenic acids are known today, and only one was known up to 1957. The main difficulty in preparing and isolating them may be related to their instability because these acids may actually be viewed as thiohydroperoxide derivatives. It is for this reason that the isolated acids should be handled with caution.

Sulfenyl chlorides are relatively easily prepared by halogenation of the disulfide and therefore serve as the main source of the starting material for the many sulfenyl derivatives prepared by nucleophilic substitution reactions [1]. In some cases, thiophenols or sulfides are used in place of the disulfides in the halogenation reaction, leading to sulfenyl halides.

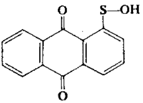
Although the absolute structure of the sulfenic acids is still to be rigorously determined, the structure of a sulfenate ester and a sulfenamide have been reported.

The sulfenyl halides also undergo reactions of addition, displacement, Friedel–Crafts, oxidation, and reduction [2]. The chemistry of sulfenium ions ($RS^+$) is presently undergoing widespread investigation as an intermediate in many reactions in sulfur chemistry [2].

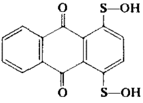
The sulfenyl compounds are of industrial interest because of the availability of the sulfenyl halides. Some sulfenyl derivatives find use in such areas as vulcanization acids [3a–c] radiation protecting group (Bunte salts or sulfenyl sulfites) [1], photosensitizers for polymerization [4], dye chemicals [5], wool chemicals [6], in polymer chemistry [7a,b] and in pesticide chemistry [8a,b], to mention only a few. For reviews on the chemistry of sulfenic acids see references [8c,d] and recent work by F. A. Davis [8e].

## 2. SULFENIC ACIDS

Sulfenic acids, R—S—OH, are bivalent compounds of sulfur. The first sulfenic acid synthesized was anthraquinone-1-sulfenic acid (I) by Fries, in 1912 [9]. For the next 45 years, attempts to synthesize other sulfenic acids failed [10a–i]; nevertheless, they were postulated as intermediates in many reactions [10j]. In 1957, Bruice and Markiw [11] described the synthesis of anthraquinone-1,4-disulfenic acid (II), which was synthesized by a route similar to (I), as shown by comparison of Eqs. (1) and (2).



(I)



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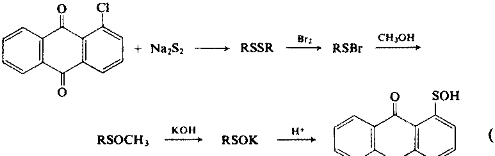
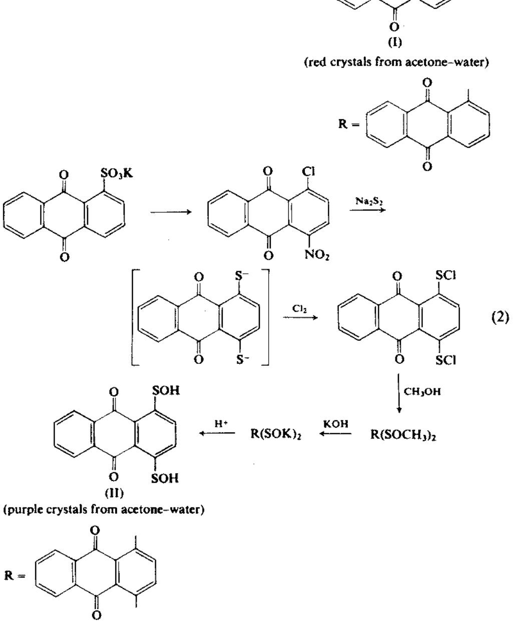


(1)

(I)

(red crystals from acetone–water)



(2)

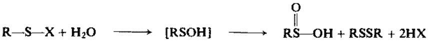
(II)

(purple crystals from acetone–water)

It is interesting to note that Fries and Schurmann [10a,b], by a synthetic route similar to Eq. (1), could not obtain the 4-hydroxy-, 4-methoxy-, or 4-amino-substituted (I) because chlorination or bromination did not afford the sulfenyl halide.

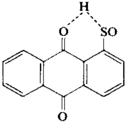
Attempts to isolate benzene- or naphthalenesulfenic acid and its substituted derivatives by a similar route were also unsuccessful [12a,b].

The hydrolysis of the sulfenyl halide with water did not afford the sulfenic acid but gave the disulfide and the sulfinic acid (Eq. 3) [13a], or the sulfonic acid and sulfenic anhydride [13b].



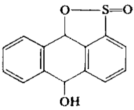
$$R{-}S{-}X + H_2O \longrightarrow [RSOH] \longrightarrow R\overset{O}{\overset{\|}{S}}{-}OH + RSSR + 2HX \qquad (3)$$

Kharasch earlier suggested that the reason for the stability of anthraquinone-1-sulfenic acid (I) may be the hydrogen bonding as shown in (III) [8c, 14]. However, this did not explain the inability to isolate 1-fluorenosulfenic acid [10h].

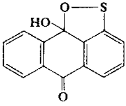


(III)

Lecher and Hardy suggested that stabilization of (I) may be due to an anthrol-type structure (IV) [15]. Rylander [16] suggested a tetracyclic structure (V) for the compound (I) based on infrared spectral data relating to the carbonyl group.



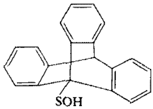
(IV)



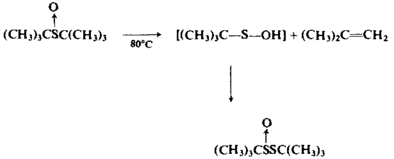
(V)

In 1958, Jenny [17a] described the synthesis of an anthraquinone-1,5-disulfenic acid, which was also made by a route similar to that of (I) or (II).

In 1983, Nakamura reported the isolation of the stable sulfenic acid 9-triptycenesulfenic acid [17b].



In 1967, Shelton and Davis [18a] reported NMR and preparative evidence for the intermediate existence of the first aliphatic sulfenic acid, *t*-butylsulfenic acid, in the thermolysis of *t*-butylsulfoxide at 80°C (Eq. 4).

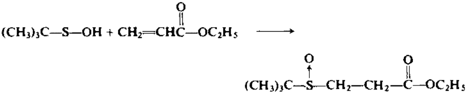


$$(CH_3)_3C\overset{\overset{O}{\uparrow}}{S}C(CH_3)_3 \xrightarrow[80^\circ C]{} [(CH_3)_3C{-}S{-}OH] + (CH_3)_2C{=}CH_2 \qquad (4)$$

$$\downarrow$$

$$(CH_3)_3C\overset{\overset{O}{\uparrow}}{S}SC(CH_3)_3$$

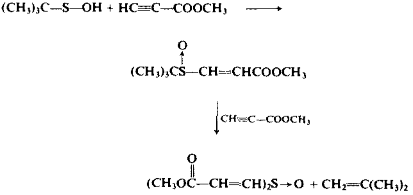
The *t*-butylsulfenic acid is trapped by its addition to electrophilic olefins at room temperatures, as shown in Eqs. (5) and (6). In the case of *t*-butylsulfenic infrared (IR) spectral data indicate it may undergo tautomerism as shown in Eq. (7).



$$(CH_3)_3C{-}S{-}OH + CH_2{=}CH\overset{\overset{O}{\|}}{C}{-}OC_2H_5 \longrightarrow$$

$$(CH_3)_3C{-}\overset{\overset{O}{\uparrow}}{S}{-}CH_2{-}CH_2{-}\overset{\overset{O}{\|}}{C}{-}OC_2H_5 \qquad (5)$$

Ethyl β(2-methylpropylsulfinyl)propionate



$$(CH_3)_3C{-}S{-}OH + HC{\equiv}C{-}COOCH_3 \longrightarrow$$

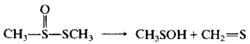
$$(CH_3)_3C\overset{\overset{O}{\uparrow}}{S}{-}CH{=}CHCOOCH_3$$

$$\Big\downarrow CH{\equiv}C{-}COOCH_3$$

$$(CH_3O\overset{\overset{O}{\|}}{C}{-}CH{=}CH)_2S{\rightarrow}O + CH_2{=}C(CH_3)_2 \qquad (6)$$

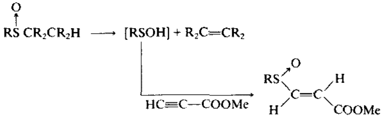
$$(CH_3)_3C{-}S{-}OH \rightleftharpoons (CH_3)_3C\overset{\overset{O}{\uparrow}}{S}H \qquad (7)$$

Methanesulfenic acid was detected by the flash -vacuum pyrolysis (FVP) microwave technique, using methyl methanethiosulfinate at 250°C. In addition, thioformaldehyde was a by-product [18b].



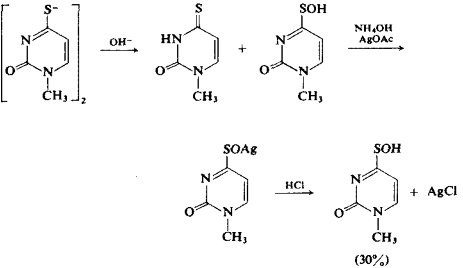
$$CH_3{-}\overset{\overset{O}{\|}}{S}{-}SCH_3 \longrightarrow CH_3SOH + CH_2{=}S \qquad (8)$$

Sulfenic acids generated in the gas phase under FVP of sulfoxide can be trapped by being deposited in a cold finger condenser (cooled in liquid nitrogen) and containing methyl propiolate [8e]. The product is a *trans*-vinyl sulfoxide [8e].



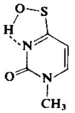
(9)

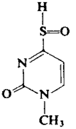
Recently, 1-methyluracil-4-sulfenic acid [19] has been claimed to be obtained in small amounts by the alkaline cleavage of bis(methyl-4-thiouridine) disulfide (Eq. 10).

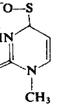


(10)

The latter sulfenic acid is probably stabilized by the following hydrogen bonding structures:


(VI)


(VII)


(VIII)

This is the first isolated sulfenic acid prepared by alkaline cleavage of a disulfide.

The preceding information shows that the three isolated sulfenic acids have been prepared by the method of Eq. (1) (Fries method) and that the others were detected by derivative formation.

The method of trapping sulfenic acid intermediates by their addition to electrophilic olefins should be capable of being applied to the many other reactions where they have been postulated but not isolated (see Eqs. 5 and 6).

The use of NMR and X-ray diffraction techniques should also be capable of better defining the structure of the (mono and di) 1-anthraquinone sulfenic acids.

Recently [20] the molecular structure of the methyl ester of *o*-nitrobenzene-sulfenic acid has been determined by X-ray diffraction and the results are shown in Fig. 1.

The X-ray diffraction results [20] indicate the following:

(a) The structure is planar with the exception of the methyl group.
(b) A short distance (2.44 Å) between S and one of the oxygen atoms of

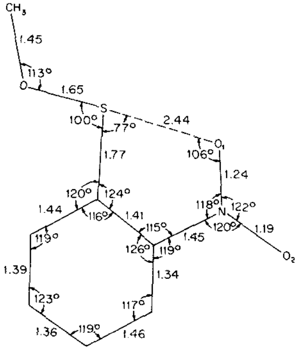


FIG. 1. Geometry of the molecular of methyl *o*-nitrobenzenesulfenate. The estimated standard deviations in the bond distances are 0.02 Å, except for S—O and C—S, where they are about 0.01. The estimated standard deviations in the bond angles are about 1.5°. With the exception of the methyl group, the molecule is planar. The methyl group is bent out of the plane as far as is consistent with the geometry indicated. [Reprinted from W. C. Hamilton and S. J. LaPlaca, *J. Amer. Chem. Soc.* **86,** 2289 (1964). Copyright 1964 by the American Chemical Society. Reprinted by permission of the copyright owner.]

the nitro group. The sum of the van der Waals radii for S and O is 3.25 Å.

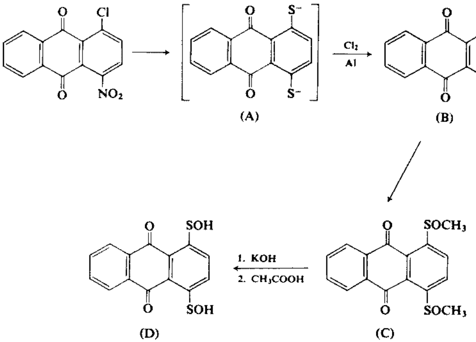
(c) There exists a single bond length between divalent sulfur and oxygen (1.648 ± 0.012 Å).

A similar study, which is still to be determined on the anthraquinonesulfenic acids, would show whether a quinone carbonyl group can also interact with the sulfur atom to give a linear O–S—O group.

In addition, the use of NMR to monitor reactions should also be capable of detecting the presence of previously postulated sulfenic acids, just as it has been used to detect the presence of *t*-butylsulfenic acid.

It is interesting to note that the related selenenic acids, R—Se—OH, have been reported to be more stable than the sulfenic acids [14].

## 2-1. *Preparation of Anthraquinone-1,4-disulfenic Acid* [11]



(11)

(*a*) *Preparation of poly(1,4-dithioanthraquinone)* (A). To a flask containing 4.40 gm (0.0152 mole) of recrystallized 1-chloro-4-nitroanthraquinone (m.p. 259°C) suspended in 400 ml of reagent grade dioxane is added 0.512 gm (0.0157 mole) of sulfur. The solution is brought to boiling and then 3.84 gm (0.0238 mole) of sodium sulfide nonahydrate dissolved in a solution of 80 ml of dioxane and 160 ml of water is added. The mixture is refluxed for 5 hr, cooled, and filtered; the solid is washed with hot dioxane, water, and then acetone, to give on drying at 80°C 3.2 gm (77%) of a brick red amorphous solid, m.p. >350°C.

(*b*) *Preparation of anthraquinone-1,4-disulfenyl chloride* (B). To a three-necked flask containing 100 ml of chloroform and a small piece of aluminum is added 2.0 gm (0.0074 mole) of poly(1,4-dithioanthraquinone). The flask is equipped with a condenser, gas inlet tube, and mechanical stirrer. While cooling in an ice bath, a small stream of chlorine gas is passed through the reaction mixture for 3 hr. The reaction mixture is stoppered, allowed to sit at room temperature for 12 hr, cooled for several hours, filtered, washed with ether, and dried, to give 2.2 gm (88%) of crude product.

(*c*) *Preparation of dimethyl anthraquinone-1,4-disulfenate* (C). Two grams (0.0059 mole) of crude anthraquinone-1,4-disulfenyl chloride are suspended in a solution of 250 ml of absolute methanol, 150 ml anhydrous benzene, and 1.0 ml of dry pyridine. The mixture is boiled until all the solid dissolves, and the mixture is allowed to stand at room temperature for 2 days. The mixture is then boiled for 5 min, cooled, a small amount of activated carbon (Norite) added, boiled for 5 min again, filtered, and concentrated to one-half volume to afford long red needles. The chilled reaction mixture (12-hr cooling) is filtered, to afford 1.0 gm (51%), m.p. 176–179°C (wet). Recrystallization from benzene–methanol and drying at 100°C for 2 hr over $P_2O_5$ at 1.0 mm Hg raises the melting point to 189–190°C.

(*d*) *Preparation of anthraquinone-1,4-disulfenic acid* (D). To a flask containing 20 ml of absolute ethanol is added 0.5 gm (0.0015 mole) of dimethyl anthraquinone-1,4-disulfenate. The suspension is brought to a boil and then 1.0 ml of 33% (0.006 mole) aqueous potassium hydroxide is added. The solution is boiled for 4 min more, and then 100 ml of hot distilled water added. The resulting clear blue solution is immediately chilled and filtered, and the filtrate is acidifield with acetic acid. The resulting purple coagulant is filtered, washed with water, redissolved in cold acetone, and filtered, and then water is added dropwise until the solution becomes cloudy. After further refrigeration water is added dropwise to complete the preparation of the product, which on drying affords 0.1–0.12 gm (22–26%). Heating the latter above 100°C causes it to turn from purple to yellow. Reaction with HCl and then methanol gives the diester derivative of the same melting point.

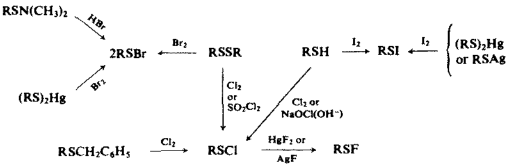
## 3. SULFENYL HALIDES

### A. Introduction

Sulfenyl halides, RSX (X = F, Cl, Br, or I), are prepared by either halogenation or hydrohalogenation reactions of sulfides, mercaptans, or sulfenamides, as shown in Scheme 1 [14, 21, 22]. The sulfenyl iodides are prepared from either the silver or mercuric mercaptides [23a,b]. Sulfenyl fluorides are prepared by an exchange reaction as shown in Scheme 1 [24].

The *Chemical Abstracts* nomenclature which is followed here describes the compounds as sulfenyl halides and not alkyl or arylsulfur halides or aryl or alkyl halosulfides [21]. The older literature sometimes also describes these compounds as thiocarbonyl chlorides or chloromercaptans.

SCHEME 1
Preparation of Sulfenyl Halides



The sulfenyl halides undergo nucleophilic reactions to give a wide variety of sulfenyl derivatives [24a,b], as shown in Eq. 12.

$$\mathrm{RSX} + \mathrm{Z}^- \longrightarrow \mathrm{RSZ} + \mathrm{X}^- \qquad (12)$$

$\mathrm{R}$ = alkyl, aryl, $\mathrm{R_2N}$, or $\mathrm{(RO)_2P(O)}$–
$\mathrm{X}$ = –Cl, –Br, –SCN, –S(O)R, –$\mathrm{S(O_2)R}$, –NHR, etc.
$\mathrm{Z}^-$ = nucleophilic reagent

Sulfenyl halides are quantitatively determined in anhydrous acetic acid by an iodiometric method involving the reaction shown in Eq. 13 [25b].

$$2\mathrm{ArSCl} + 2\mathrm{I}^- \longrightarrow \mathrm{ArSSAr} + \mathrm{I_2} + 2\mathrm{Cl}^- \qquad (13)$$

2,4-Dinitrobenzenesulfenyl chloride has been reported to be a useful reagent for the characterization of alcohols, mercaptans, amines, hydroxysteroids, olefin oxides, aromatic compounds, olefins, and ketones [26]. The preparation of this sulfenyl chloride is described in Procedures 3-4 and 3-5.

Furthermore, sulfenyl halides also undergo addition reaction (to olefins [26a–f], diolefins [26a–f], allenes [27], and acetylenes [28]) displacement reactions, oxidations, reduction, Friedel–Crafts [29] and free-radical reactions [2, 22, 30a–g], etc. Sulfenyl halides are also important in producing sulfenium ions, $\mathrm{RS}^+$ [31], and many mechanistic efforts have been made to study this intermediate. Sulfenyl halides are also important industrially (radiation protective agents, wool modification preparation of novel heterocyclic compounds, and in rubber chemistry) as described in Section 1.

## B. Sulfenyl Halides from Disulfides

Disulfides react with chlorine or bromine at relatively low temperatures in anhydrous nonreactive nonpolar solvents ($\mathrm{CCl_4}$, $\mathrm{CHCl_3}$, $\mathrm{CH_2Cl{—}CH_2Cl}$, $\mathrm{C_6H_5}$, $\mathrm{C_5H_{12}}$), to give the sulfenyl halides in good-to-excellent yields (Eqs. 15, 16]. The reaction appears to be an electrophilic process because it is catalyzed by Friedel–Crafts catalysts and sulfuric acid [32]. However, at elevated temperatures, a free-radical process is also operative. Sulfuryl chloride is a more effective chlorinating agent than chlorine gas [26a].

$$\overset{+}{\mathrm{Cl}}\text{—}\overset{-}{\mathrm{Cl}} + \mathrm{RS\text{—}SR} \longrightarrow \mathrm{RSCl} + \mathrm{RS}^+ + \mathrm{Cl}^- \qquad (14)$$

$$\mathrm{RS}^+ + \mathrm{Cl}^- \longrightarrow \mathrm{RSCl} \qquad (15)$$

Sulfuric acid catalysis probably works as follows (Eqs. 16–18) [33]:

$$\mathrm{RS\text{—}SR} + \mathrm{H}^+ \rightleftharpoons \mathrm{RS}^+ + \mathrm{RSH} \qquad (16)$$

$$\mathrm{RS}^+ + \mathrm{Cl}_2 \longrightarrow \mathrm{RSCl} + \mathrm{Cl}^+ \qquad (17)$$

$$\mathrm{Cl}^+ + \mathrm{RSSR} \longrightarrow \mathrm{RSCl} + \mathrm{RS}^+ \qquad (18)$$

Bromination and iodination should follow a mechanism similar to that shown in Eqs. 14–18.

Rathke in 1873 [34a] appears to have reported the first synthesis of a sulfenyl chloride—that is, trichloromethanesulfenyl chloride by the action of chlorine on carbon disulfide.

$$3\mathrm{Cl}_2 + \mathrm{CS}_2 \xrightarrow{\mathrm{I}_2} \mathrm{CCl_3SCl} + \mathrm{SCl}_2 \qquad (19)$$

More recent work reports the use of sulfuric acid and hydrochloric acid as catalysts for this reaction when carried out in aqueous media [34b]. This compound is also known as perchloromethylmercaptan. The use of activated carbon to catalyze this reaction has also been reported [34c,d].

Zincke [10c,e–g, 12a, 35], in 1909–1918, reported the preparation of many aryl sulfenyl chlorides.

The synthesis of a sulfenyl iodide (2-benzothiazolesulfenyl iodide) has been reported in a patent [36].

The halogenation reaction, if carried too far, will result in the formation of tetrahalogen derivatives [37]. Furthermore, chlorination or bromination of aryl disulfides sometimes results in halogenation of the aromatic ring or aliphatic side chain in preference to scission of the disulfide linkage [10b, 38–40].

Zincke [40] reported that the bromination in carbon tetrachloride of the nitrophenyl disulfide afforded the following sulfenyl bromides: $\mathrm{BrSC_6H_4NO_2}$ and $\mathrm{BrSC_6H_3MeNO_2}$. However, the bromination of diphenyl disulfide affords $\mathrm{BrC_6H_4SSC_6H_4Br}$ and not $\mathrm{BrSC_6H_5}$.

Aliphatic disulfides also are halogenated in the alkyl portion. This accounts for the few reported syntheses of pure aliphatic sulfenyl chlorides [38].

For example, methanesulfenyl chloride is prepared by chlorination of methyl sulfide at −20°C (Eq. 20) [41a,b]. The ethyl, propyl, isopropyl, and

$$CH_3SSCH_3 + Cl_2 \longrightarrow 2CH_3SCl \qquad \begin{array}{l}\text{b.p. } 27^\circ\text{–}28^\circ\text{C}\\ (50\text{–}60 \text{ mm Hg})\end{array} \tag{20}$$

*n*-butyl compounds have been made by a similar method [42a,b]. The use of excess chlorine first affords chloromethylsulfenyl chloride [41a,b] and eventually trichloromethylsulfenyl chloride (Eq. 21) [43].

$$\begin{array}{l} CH_3SSCH_3 + 2Cl_2 \longrightarrow 2Cl\text{—}CH_2SCl \xrightarrow{Cl_2} \\ \qquad\qquad Cl_2CHSCl \xrightarrow{Cl_2} CCl_3SCl \end{array} \tag{21}$$

Chloromethylsulfenyl chloride can also be made by the photolytic decomposition of methanesulfenyl chloride [44].

When *t*-alkyl disulfides are used chlorination cleaves them at the S—C bond rather than the S—S bond (Eq. 22) [45].

$$(CH_3)_3CS\text{—}SC(CH_3)_3 \xrightarrow{Cl_2} (CH_3)_3CSS\text{—}Cl + (CH_3)_3C\text{—}Cl \tag{22}$$

Nitro or carboxyl groups in the aromatic nucleus tend to retard aryl halogenation. However, the preparation of benzenesulfenyl chloride tends to give some ring chlorination. The chlorination of dilute solutions at low temperatures with the exclusion of light gives very little ring chlorination.

Several examples of the preparation of alkyl and aryl sulfenyl halides from disulfides, along with preparative details, are described in Table I.

The aromatic sulfenyl chlorides are more stable than the aliphatic sulfenyl chlorides. For example, it has been reported that a solution of benzenesulfenyl chloride in carbon tetrachloride does not decompose after 2 months at room temperature, whereas a solution of cyclohexanesulfenyl chloride at the same starting molar concentration and temperature in carbon tetrachloride has a half-life of only 7 hr [46].

### *3-1. Preparation of Methanesulfenyl Chloride* [47]

$$CH_3SSCH_3 + SO_2Cl_2 \longrightarrow 2CH_3SCl + SO_2 \tag{23}$$

To a flask containing 23.6 gm (0.25 mole) of dimethyl disulfide at −15° to −20°C is slowly added dropwise 34 gm (0.25 mole) of freshly distilled

## TABLE I

### PREPARATION OF SULFENYL HALIDES BY THE HALOGENATION OF DISULFIDES

| RSSR (moles), R = | Halogen reagent (moles) | Solvent (ml) | Catalyst | Reaction conditions Temp. (°C) | Time (hr) | Yield (%) | B.p., °C (mm Hg) or m.p., °C | $n_D$ (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| $CH_3$<br>(0.25) | $SO_2Cl_2$<br>(0.20) | — | — | −20 to −15 | 1 | 90 | 27–28<br>(53–60) | —[a] | *b* |
| (0.25) | $Cl_2$<br>(0.48) | — | — | −20 to −15 | 1 | — | 27–28<br>(53–60) | —[a] | *c* |
| $(CH_3)_3C$<br>(0.75) | $Cl_2$<br>(0.75) | Isopentane<br>(1000) | — | 30–35 | 1 | 85 | — | — | *d* |
| $Cl—CH_2CH_2$-<br>(2.37) | $Cl_2$<br>(2.38) | $CCl_4$<br>(1000) | — | 10 | 2–3 | 57–79 | 47–47.5<br>(15) | 1.5290<br>(20) | *e* |
| $CH_3CONHCH_2CH_2$<br>(0.00848) | $Cl_2$<br>(0.00848) | $CH_2Cl_2$<br>(75) | — | −35 | ½ | 55 | — | — | *f* |
| $C_6H_5$<br>(0.15) | $SO_2Cl_2$<br>(0.15) | $CH_2Cl_2$<br>(100) | Pyridine<br>(3 ml) | 25 | 2 | 76 | 49 (4) | 1.6130<br>(20) | *g* |
| *o*-$NO_2C_6H_4$<br>*(0.5)* | $Cl_2$<br>*(1.0)* | $CCl_4$<br>*(600)* | $I_2$<br>*(0.25 gm)* | 50–60 | 2–2½ | 96–97 | 73–74.5 | — | *h* |
| 2,4-$(NO_2)_2C_6H_5$<br>(0.25) | $Cl_2$<br>(0.25) | $CH_2Cl—CH_2Cl$<br>(250) | Fe<br>(0.15 gm) | 120 | 1–1½ | 60 | 95–95.5 | — | *i* |
| (0.25) | $SO_2Cl_2$<br>(1.14) | $CCl_4$<br>(600) | Pyridine<br>(5 ml) | 77 | 3–5 | 82.5 | 97–98 | — | *j* |
| 2-$(NO_2)$-4-(COOH)-$C_6H_3$)<br>(0.055) | $Cl_2$<br>(0.06) | $CH_2Cl—CH_2Cl$<br>(1400) | 30% fuming<br>(1.5 ml) | 25–120 | ½–1 | 65 | 183–185 | — | *k* |
| 2,4-$(NO_2)_2C_6H_3$<br>(0.0125) | $Br_2$<br>(0.056) | $CH_2Cl—CH_2Cl$<br>(15) | $AlBr_3$<br>(1.0 gm) | 20–25 | 3 | 86 | 104.5–105.5 | — | *i* |

[a] The NMR shows a singlet at 2.91 ppm ($CH_3SSCH_3$ shows a singlet at 2.41 ppm).

[b] W. H. Mueller and P. E. Butler, *J. Amer. Chem. Soc.* **90**, 2075 (1968).

[c] H. Brintzinger, K. Pfannstiel, H. Koddebusch, and K. E. Kling, *Chem. Ber.* **83**, 87 (1950).

[d] W. A. Schulze, G. H. Short, and W. W. Crouch, *Ind. Eng. Chem.* **42**, 916 (1950).

[e] R. C. Fuson, C. C. Price, R. A. Bauman, O. H. Bullitt, Jr., W. R. Hutchard, and E. W. Maynert, *J. Org. Chem.* **11**, 469 (1946).

[f] N. E. Heimer and L. Field, *J. Org. Chem.* **35**, 3012 (1970).

[g] W. H. Mueller and P. E. Butler, *J. Amer. Chem. Soc.* **90**, 2075 (1968).

[h] M. H. Hubacher, *Org. Syn. Coll.* **2**, 455 (1943); H. Kwart, R. K. Muller, and J. L. Nyce, *J. Amer. Chem. Soc.* **80**, 887 (1958).

[i] N. Kharasch, G. I. Gleason, and C. M. Buess, *J. Amer. Chem. Soc.* **72**, 1796 (1950).

[j] D. Lawson and N. Kharasch, *J. Org. Chem.* **24**, 857 (1959).

[k] A. J. Havlik and N. Kharasch, *J. Amer. Chem. Soc.* **77**, 1150 (1955).

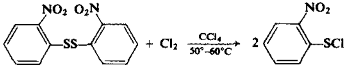
sulfuryl chloride while keeping the temperature at −15° to −20°C. The reaction mixture is stirred for 1 hr, and then distilled to afford 37.1 gm (90%), b.p. 27–28°C (53–60 mm Hg); NMR, 2.91 ppm (singlet). The crude product can also be used without distillation since most of the material is product.

### *3-2. Preparation of Benzenesulfenyl Chloride* [47]

$$C_6H_5SSC_6H_5 + SO_2Cl_2 \longrightarrow 2C_6H_5SCl + SO_2 \tag{24}$$

To a flask containing 32.7 gm (0.15 mole) of diphenyl disulfide dissolved in 100 ml of dichloromethane containing 3 ml of pyridine is slowly dropwise added at room temperature 20.3 gm (0.15 mole) of freshly distilled sulfuryl chloride. After completion of the addition, the solution is stirred for an additional hour, concentrated under reduced pressure (12 mm Hg) at 25°C, and the residue distilled to afford 33 gm (76%), b.p. 49°C (4 mm Hg), $n_D^{20}$ 1.613 [48], of a dark red liquid.

### *3-3. Preparation of 2-Nitrobenzenesulfenyl Chloride* [49]



(25)

**CAUTION:** This chloride is explosive, and the solvent has to be removed under reduced pressure.

To a 500-ml, three-necked flask equipped with a mechanical stirrer, thermometer, gas addition tube, and condenser is added 200 ml of dry carbon tetrachloride, 30 gm (0.1 mole) of 2,2′-dinitrophenyl disulfide, and 0.05 gm of iodine as a catalyst. The suspension is heated to 50–60°C, and chlorine gas is added at such a flow rate that 10 gm (0.14 mole) is added over a 2–2½-hr period at this temperature. After this time, the solid starting disulfide finally goes into solution, and the warm dark yellow solution is filtered. The solution is cooled to 5°C, and the product that crystallizes out is filtered and dried to afford 25.2–27.0 gm (66–71%), m.p. 73–74.5°C.

Some additional product may be obtained by concentration of the mother liquor under reduced pressure. The resulting oil is dried further at 50°C and then crystallizes to afford an additional 9.6–11.6 gm. Therefore, the total yield is 34.8–38.6 gm (96–97%).

NOTES: (a) *o*-Nitrobenzenesulfenyl chloride decomposes with moisture or when heated to 170°C. If the material is stored in a well-sealed brown, glass-stoppered bottle, it is stable for many months. The material can be

TABLE II

PREPARATION OF SULFENYL CHLORIDES BY THE ACTION OF CHLORINE ON ARYL DISULFIDES

| Product $RArSCl$, R = | Yield (%) | B.p., °C (mm Hg) or m.p., °C | Ref. |
|---|---|---|---|
| H | 100 | 58 (3) | *a* |
| *o*-$CH_3$ | 87 | 99 (16) | *a* |
| *p*-$CH_3$ | 85 | 77.5–78.5 (2.5) | *a* |
| *o*-$OCH_3$ | 62 | 126–127 (14) | *a* |
| *p*-$OCH_3$ | 76 | 128–130 (17) | *a* |
| *o*-Cl | 94 | 116 (17) | *a* |
| *m*-Cl | 90 | 118 (21) | *a* |
| *p*-Cl | — | 94 (6) | *a* |
| *m*-$NO_2$ | — | 120 (1) | *b* |
| *p*-$NO_2$ | — | 50–52 | *b* |

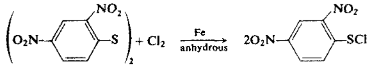
[a] F. Montanari, *Gazz. Chim. Ital.* **86**, 406 (1956).

[b] M. Raban and F. B. Jones, Jr., *J. Amer. Chem. Soc.* **93**, 2692 (1971).

recrystallized from carbon tetrachloride (2 ml/gm) by filtering, cooling to 5°C, filtering, and drying to give the product, m.p. 70–73°C, in 75% recovery. (b) A similar method has been used by Zincke [40] to prepare *o*-nitrobenzenesulfenyl chloride. The same method can also be used to prepare the following sulfenyl halides [49]: *o*-nitro-*p*-chlorobenzenesulfenyl chloride, m.p. 95–97°C; 2,4-dinitrobenzenesulfenyl chloride, m.p. 94–95°C.

Other sulfenyl chlorides reported to be prepared by Procedure 3-3 are shown in Table II.

### 3-4. *Preparation of 2,4-Dinitrobenzenesulfenyl Chloride by the Chlorinolysis of 2,4-Dinitrophenyl Disulfide* [44]



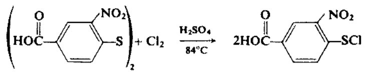
(26)

**CAUTION:** *This reaction should be carried out in a hood behind a* safety shield. The product decomposes explosively if heated above 90–100°C [50].

To a 500-ml, three-necked flask equipped with a mechanical stirrer, distillation column, and distillation head is added 100 gm (0.25 mole) of dry 2,4-dinitrophenyl disulfide and 250 ml of ethylene chloride. The contents are heated with an oil bath at 125°C until 30–40 ml of the solvent is collected by distillation. The contents are cooled and the distillation head replaced by a gas inlet and exit tube connected to an alkali trap. Then 0.15 gm (0.002 mole) of Merck "Iron by Hydrogen" powder is added as a catalyst [51a–c], and dry chlorine gas is slowly bubbled into the reaction. In a few minutes, the reaction warms up, and the flask is surrounded with a 20°C water bath. The chlorine gas is bubbled in at such a rate that 18 gm (0.25 mole) is added over a 1–1½-hr period. After this time, the suspended disulfide should gradually disappear, and a clear, amber-red solution results. The flow of chlorine gas is stopped, the solution stirred for 1 hr, filtered through diatomaceous earth, the filtrate aspirated to remove excess chlorine, and then 400 ml of anhydrous ether is added. Within ½ hr, most of the product crystallizes by cooling the flask in an ice–salt-water bath for 3–4 hr. The product is filtered, washed with 100 ml of cold ether, and then dried to afford 70 gm (60%) of brilliant yellow needles, m.p. 95–95.5°C.

NOTES: Six drops of fuming sulfuric acid can also be used in place of iron as a catalyst in this reaction to give equal or better yields of the sulfenyl chloride product. The reaction also can be run in other solvents such as methylene chloride or carbon tetrachloride.

### *3-5. Preparation of 4-Carboxyl-2-nitrobenzenesulfenyl Chloride* [52]

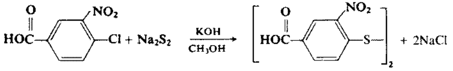


(27)

**CAUTION:** Use a well-ventilated hood and a safety shield.

To a 3-liter, three-necked flask equipped with a Vigreux column, distillation head, and stirrer is added 22 gm (0.131 mole) of bis(2-nitro-4-carboxyphenyl) disulfide and 1400 ml of dry ethylene dichloride. Approximately 150 ml of solvent is distilled to ensure fully anhydrous conditions. The flask is then reequipped with a gas inlet and outlet tube condenser and stirrer. Then 1.5 ml of 30% fuming sulfuric acid is added and chlorine gas addition is started at a vigorous rate. In approximately 20 min, a clear solution results, which is then filtered. The filtrate is concentrated under reduced pressure to afford 17.0 gm (65%), m.p. 183–185°C (dec.) of a yellow crystalline solid. The product is recrystallized from ethylene dichloride.

The starting disulfide [52] is prepared by the reaction of sodium sulfide and sulfur in methanol with 3-nitro-4-chlorobenzoic acid in methanolic potassium hydroxide (Eq. 28).



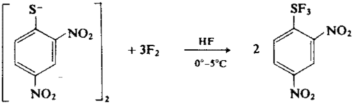
(28)

### 3-6. *Preparation of Trichloromethanesulfenyl Fluoride* [24]

$$2CCl_3SCl + HgF_2 \xrightarrow[25^{\circ}C]{CH_2Cl_2} 2CCl_3SF + HgCl_2 + \text{some } CCl_3SClF_2 + (CCl_3S)_2S \qquad (29)$$

To a flask containing 90 gm (0.48 mole) of trichloromethanesulfenyl chloride in 200 ml of dichloromethane is added portionwise 100 gm (0.42 mole) of mercuric fluoride, keeping the temperature at 25°C. The reaction is slightly exothermic, and after the addition, the reaction mixture is refluxed for 3 hr. Then the reaction mixture is filtered and the filtrate fractionally distilled to afford 42.2 gm (51.5%) of trichloromethanesulfenyl fluoride, b.p. 99–101°C (760 mm Hg), $n_D^{25}$ 1.4852, and another fraction 22.05 gm, b.p. 65°C (50 mm Hg) and 127°C (7 mm Hg). A third fraction is also obtained, b.p. 128–133°C (7 mm Hg), which solidifies on standing. Recrystallization of the third fraction from ethanol affords white needles of bis(trichloromethyl) trisulfide, m.p. 54.5°C. Redistillation of the second fraction affords trichloromethyl sulfur difluoro chloride, b.p. 151.5–153.5°C (760 mm Hg), $n_D^{25.5}$ 1.5675 and bis(trichloromethyl) disulfide, b.p. 156–157°C (10 mm Hg).

Direct fluorination of bis(2,4-dinitrophenyl) disulfide in liquid hydrogen fluoride at 0–5°C does not give the sulfenyl fluoride but 2,4-dinitrophenyl sulfur trifluoride in 51% yield (Eq. 30) [53]. The latter compound is surprisingly stable and has been characterized. The fluorination of 2,4-dinitrophenol gave only tarry products.



(30)

The reaction of 2,4-dinitrobenzenesulfenyl fluoride with mercuric fluoride or antimony fluoride did not give the corresponding sulfenyl fluoride [53].

Kober [24] found that trichloromethanesulfenyl fluoride and heptafluoro-*n*-propanesulfenyl fluoride could be prepared in good yield by reaction of the corresponding sulfenyl chlorides with mercuric fluoride or silver fluoride in refluxing dichloromethane. The application of this method to the preparation of aromatic sulfenyl fluorides was not successful, as described previously.

### C. Sulfenyl Halides from Thiopenols and Mercaptans

Chlorine or bromine react with thiophenols or mercaptans under mild conditions to give the sulfenyl chloride or bromide [10a,c, 54–58]. A side reaction gives the disulfide by reaction of the sulfenyl halide with thiophenol [10c, 23a, 55, 57, 59–62]. The disulfide can react with excess halogen to give the sulfenyl halide as shown in Eqs. 31 and 32. Ring halogenation can also take place under more vigorous conditions.

$$\mathrm{RSH} + \mathrm{X_2} \longrightarrow \mathrm{RSX} + \mathrm{HX} \tag{31}$$

$$\mathrm{RSX} + \mathrm{RSH} \xrightarrow{-\mathrm{HX}} \mathrm{RSSR} \xrightarrow{\mathrm{X_2}} 2\mathrm{RSX} \tag{32}$$

In order to avoid disulfide formation (Eq. 33), one should carry out the reaction at room temperature and add the thiphenol or mercaptan dropwise to the halogen dissolved in carbon tetrachloride or chloroform [55, 63]. The addition of one or two crystals of iodine catalyzes the reaction. If the chlorination is carried out in glacial acetic acid, the product obtained is the sulfonyl chloride [59, 64, 65]. The halogenation of mercuric mercaptides also gives the sulfenyl halide, as shown in Eq. 33 [56, 66–66]. For example, *t*-butylmercuric mercaptide reacts with bromine or iodine to give the corresponding sulfenyl halides [23a, 60, 67a].

$$(\mathrm{RS})_2\mathrm{Hg} + 2\mathrm{X_2} \longrightarrow 2\mathrm{RSX} + \mathrm{HgX_2} \tag{33}$$

Recently, the preparation of tetrachloro-*p*-xylylene bissulfenyl chloride in 89% yield has been described by the uncatalyzed chlorination of the corresponding bismercaptan [67b]. The use of sulfonyl chloride in place of chlorine has been described for related compounds [67b].

The use of other halogenating agents is described in the Miscellaneous Methods section.

#### *3-7. General Procedure for the Preparation of Arenesulfenyl Chlorides by the Chlorination of Thiols* [55, 63, 67a]

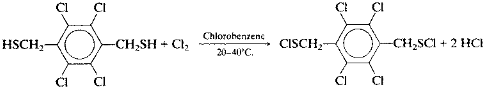
To 10 gm (0.14 mole) of chlorine dissolved in 300 ml of cold anhydrous carbon tetrachloride containing one or two crystals of iodine is added dropwise over a period of 1 hr 0.06 mole of the thiol dissolved in 50 ml of

TABLE IIA
SULFENYL CHLORIDES PREPARED BY THE CHLORINATION OF THIOLS
[55, 63, 67]

| $R—C_6H_4SCl$, R = | B.p., °C (mm Hg) | $n_D^{20}$ | Yield (%) |
|---|---|---|---|
| H– | 55 (1.0) | — | — |
| p-$CH_3O$– | 70–72 (0.3) | — | — |
| p-Cl– | 68–69 (0.5) | — | — |
| m-Cl– | 90 (2) | — | — |
| m-$CH_3$– | 90–91 (0.1) | — | — |
| p-$CH_3$– | 66–68 (0.8) | 1.6018 | 77–78 |

carbon tetrachloride. The reaction mixture is stirred for $\frac{1}{2}$ hr, and the solvent and excess chlorine removed under reduced pressure to afford an orange-red unstable liquid. The rate of reaction is followed by checking whether the 4.0 μ absorption of the S—H bond in the IR spectrum has disappeared. Rapid distillation of the crude product affords the sulfenyl chloride. Some sulfenyl chlorides prepared by this method are listed in Table IIA.

### *3-8. Preparation of Tetrachloro-*p*-Xylylene Bis-Sulfenyl Chloride* [67b]



(34)

To a mixture of 61.6 gm (0.3 mole) of tetrachloro-*p*-xylylene bismercaptan in 300 ml of chlorobenzee at 20–40°C is added chlorine gas while hydrogen chloride is evolved. The addition is continued until the weight increase is 16.0 g (0.22 mole). The mixture is stirred for 1 hr at 25–40°C and then heated to 95°C, to give a clear yellow solution. On cooling to 0–10°C, a precipitate of yellow crystals formed, which, upon filtration, yielded 67 g (89% yield), m.p. 169–170°C.

| Analysis | | |
|---|---|---|
| Analysis | (Calculated) for $C_8H_4Cl_6S_2$: | C, 25.46; H, 1.06; Cl, 56.50; S, 16.98. |
| | (Actual) | C, 26.1; H, 1.1; Cl, 56.1; S, 16.6. |

The Mol. Wt. by mass spectrometry found was 374 (chlorine isotope 35).

The same product is obtained when $SO_2Cl_2$ was used in place of chlorine and when chlorobenzene was replaced by either methylene chloride, chloroform, or carbon tetrachloride.

## D. Sulfenyl Halides from Sulfides

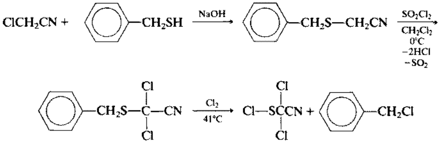
This is a less commonly used and generally poor method for the preparation of sulfenyl halides. Zincke first used this method for the preparation of aryl sulfenyl chlorides by the reaction of chlorine with aryl benzyl sulfides, as shown in Eqs. 35 and 36.

$$C_6H_5CH_2SC_6H_4C_6H_4SCH_2C_6H_5 + 2Cl_2 \longrightarrow ClSC_6H_4C_6H_4SCl + 2C_6H_5CH_2Cl \qquad (35)$$

$$4,6\text{-}Cl_2C_6H_2(SCH_2C_6H_5)_2\text{-}1,3 + 2Cl_2 \longrightarrow 4,6\text{-}Cl_2C_6H_2(SCl)_2\text{-}1,3 + 2C_6H_5CH_2Cl \qquad (36)$$

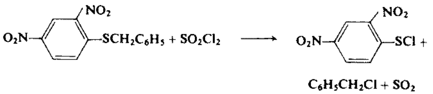
The method has found some limited use for the benzyl sulfides because they are easily cleaved by chlorine. The usefulness of this method is illustrated in Table III and in Preparation 3-9.

This technique has been used to prepare various sulfenyl chlorides by the preferential cleavage of benzyl sulfides. For example, α, α-dichloro-α-(chloromercapto) acetonitrile was reported to be prepared as follows [68c]:



(37)

### 3-9. *Preparation of 2,4-Dinitrobenzenesulfenyl Chloride by the Reaction of Sulfuryl Chloride with 2,4-Dinitrophenyl Benzyl Sulfide* [68a,b]



(38)

## TABLE III
PREPARATION OF SULFENYL HALIDES BY THE HALOGENATION OF SUBSTITUTED BENZYL SULFIDES

| $R—SCH_2C_6H_5$ (moles), R = | Halogenation reagent (moles) | Solvent (ml) | Reaction conditions: Temp. (°C) | Reaction conditions: Time (hr) | Yield (%) | M.p. (°C) | Ref. |
|---|---|---|---|---|---|---|---|
| o-$NO_2—C_6H_4$<br>(0.05) | $SO_2Cl_2$<br>(0.05) | $CCl_4$<br>(25) | 25–45 | 1/4 | 82 | 73–74 | *a* |
| 2,4$(NO_2)_2C_6H_3$<br>(0.80) | $SO_2Cl_2$<br>(0.88) | $CH_2Cl–CH_2Cl$<br>(400) | 10–15 | 1/10 | 80–90 | 95–86 | *a, b* |
| 1-Anthraquinonyl<br>(0.066) | $SO_2Cl_2$<br>(0.066) | $C_6H_6$<br>(800) | 25–45 | $\frac{1}{2}$–1 | 99 | 220–223 | *a* |
| 2,4$(NO_2)_2C_6H_3$<br>(0.8) | $Br_2$<br>(0.80) | $CCl_4$<br>(1000) | 20–25 | $\frac{1}{2}$–1 | 75–80 | 102–104 | *a, b* |

[a] N. Kharasch and R. B. Langford, *J. Org. Chem.* **28**, 1903 (1963).

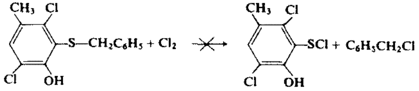
[b] N. Kharasch and R. B. Langford, *Org. Syn.* 44, 47 (1964).

**CAUTION:** This reaction should be run in a hood behind a safety shield. 2,4-Dinitrobenzenesulfenyl chloride explosively decomposes when heated above 90–100°C.

To a 1-l, three necked flask equipped with a condenser and mechanical stirrer is added at room temperature 232 gm (0.8 mole) of dry 2,4-dinitrophenyl benzyl sulfide (see Note a), 400 ml of dry ethylene chloride, and then 119 gm (0.88 mole) of sulfuryl chloride. The reaction is mildly exothermic, and the solid dissolves quickly (1–2 min) as the temperature rises to 30–35°C (see Note b). The clear solution is concentrated under reduced pressure in glass equipment only by gently heating (see Caution) with a water bath to 50–60°C to give an oil. The resulting oil is mixed with 3–4 volumes of dry petroleum ether (b.p. 30–60°C) to give a crystalline solid. The crystalline solid is filtered, washed with fresh petroleum ether, and dried, to afford 160 gm (86%), m.p. 95–96°C. Benzyl chloride 85 gm (95.5%) was obtained by concentrating the petroleum ether filtrate and washings.

NOTES: (a) 2,4-Dinitrophenyl benzyl sulfide is prepared in 81–86% yeild by reacting 202 gm (1.0 mole) of 2,4-dinitrochlorobenzene in 400 ml of methanol with 124 gm (1.0 mole) of benzyl mercaptan and 87 gm (1.1 mole) of pyridine by refluxing the mixture for 16 hr. The sulfide which precipitates on cooling, is filtered, washed with methanol, and dried to afford 235–250 gm, m.p. 128–129°C (yellow crystalline solid). (b) If the reaction does not start immediately, then add 1 drop of pyridine and gently warm to initiate the reaction.

However, some substituted benzyl sulfides are cleaved with great difficulty or not all, as shown in Eq. (39) [69]. As with the case of disulfides, the use of glacial acetic acid as the solvent in place of inert solvents give sulfonyl chlorides in the chlorination process [57–66].

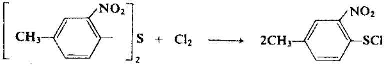


(39)

The use of other aryl sulfides such as methyl phenyl sulfide gives alkyl chlorination, as seen in Eq. 40 [40]. As mentioned earlier, the presence of

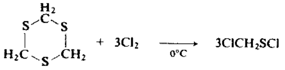
$$C_6H_5SCH_3 + Cl_2 \longrightarrow C_6H_5SCCl_3 \qquad (40)$$

nitro groups in the aromatic ring helps to reduce ring and side chain chlorination, as seen in Eq. 41 [66].



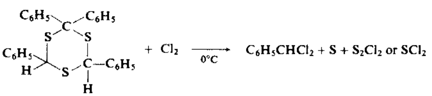
(41)

The chlorination of *s*-trithiane affords low yields of chloromethylsulfenyl chloride (Eq. 42) [70] or dichloromethylsufenylchloride [71]. The use of



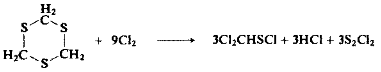
(42)

alkyl-substituted *s*-triazines gives low yields of mixtures of products. Aryl-substituted *s*-trithianes do not give sulfenyl chlorides (Eq. 43) [70].



(43)

### *3-10. Preparation of Dichloromethanesulfenyl Chloride* [72]



(44)

To an ice-cooled dry flask containing 25.0 gm (0.18 mole) of *s*-trithiane is slowly added dry chlorine gas. As soon as the solid liquefies, the temperature is raised to 10–20°C, and approximately a total of 57.0 gm (0.80 mole) of chlorine gas is absorbed. The product is distilled under reduced pressure to afford 9.9–12.9 gm (46–60%), b.p. 30°C (10 mm Hg), $n_D^{20}$ 1.5389.

## 4. SULFENAMIDES

### A. Introduction

The first reported synthesis of sulfenamides was by Zincke [40] and Lecher [56, 73–76], who found that they are produced by the reaction of sulfenyl chlorides with amines (Eq. 45). The sulfenamides are easily

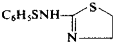
$$C_6H_5SCl + RNH_2 \longrightarrow C_6H_5SNHR \tag{45}$$

cleaved by hydrochloric acid to give the amine hydrochloride and the sulfenyl chloride (Eq. 47). Thus, sulfenamides may find use as protective groups for amines or amino groups in amino acids [74]. The preparation and chemistry of sulfenamides have recently been reviewed [75a].

$$C_6H_5SNHR + 2HCl \longrightarrow C_6H_5SCl + RNH^+Cl^- \tag{46}$$

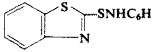
Other less important methods reported useful for the synthesis of sulfenamides are summarized in Scheme 2. Whether all of these are effective methods requires further preparative investigation for verification of reported claims. Other methods are given in the Miscellaneous Methods section.

The nomenclature [84a] of sulfenamides is illustrated as follows:



N-2-Thiazolylbenzenesulfenamide

(IX)



N-Cyclohexyl-2-benzothioazolesulfenamide

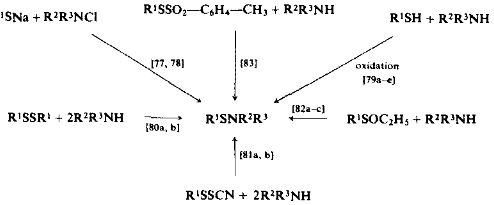
(X)

NMR experiments have shown that the unsymmetrical sulfenamide $R^1SNR^2R^4$ is dissymmetric and the chirality of this moiety is due to the restricted rotation about the N—S bond rather than the nitrogen atom's slow inversion [85a,b].

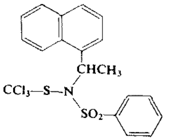
Raban and Lauderback [86] have recently reported NMR, ORD and CD

SCHEME 2

Miscellaneous Methods for the Preparation of Sulfenamides



spectra of the following optically active sulfenamide (XI), whose absolute configuration was determined using single-crystal X-ray diffraction.



(XI)

2-Benzothiazole sulfenamides have come to be commercially important as rubber vulcanization accelerators, as additives for lubricating oils, and for fungicides [84b].

Unsubstituted aliphatic sulfenamides of ammonia ($RSNH_2$) can not be isolated but can be trapped by reaction with aromatic aldehydes and ketones [75b]. Some aliphatic chloro- and fluorosubstituted sulfenamides ($CF_3SNH_2$, $CF_2ClSNH_2$, $CFCl_2SNH_2$, $RCCl_2SNR'R''$) have been isolated [75c,d,h]. The electron-withdrawing groups (halogen or aromatic) appear to stabilize the sulfenamides of ammonia.

Sulfenamides ($RSNR'R''$) have been reported to be used as sulfenyl transfer reagents in the synthesis of sulfides, disulfides, trisulfides, sulfenate esters, and other sulfenamides [75b]. The *N*-alkylidenearene sulfenemides ($RSN{=}CR'R''$) have been reported to be oxidized to arenesulfonyl-3-phenyloxiziridines and sulfinamides [75b].

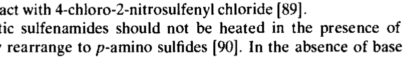
## B. *Sulfenamides from Sulfenyl Halides*

### a. THE USE OF AROMATIC SULFENYL CHLORIDES

The reaction of aromatic sulfenyl chlorides with amines to give sulfenamides was first reported by Zincke [73] and Lecher [55] and later extended by Billman and O'Mahony [87] as a means of identifying amines. This method is still the most important method of preparing sulfenamides.

Billman and O'Mahony found that *o*-nitrobenzenesulfenyl chloride, which does not react with water or alcohols, reacted well in ether, with primary and secondary aliphatic amines and aromatic amines, but not with *o*-nitroaniline or diphenylamine. The reaction with tertiary amines was not reported. 2,4-Dinitrobenzenesulfenyl chloride [88] reacts in a similar fashion, and both react with amines in aqueous solution having a concentration of 30% of the amine. Gebauer-Fülnegg reported that 4-chloro-2-nitrobenzenesulfenyl chloride reacts with diphenylamine to give the corresponding sulfenamide [89]. In addition, he reported that 2,4,6-trichloroaniline, 2,4,6-tribromoaniline, and 2,4-dichloro-1-naphthylamine did not react with 4-chloro-2-nitrosulfenyl chloride [89].

Aromatic sulfenamides should not be heated in the presence of base since they rearrange to *p*-amino sulfides [90]. In the absence of base they are stable and can recrystallize unchanged from several solvents. However, heating them to 150–160°C for several hours will cause them to rearrange (Eq. 47). Some typical examples and properties of sulfenamides prepared from sulfenyl chlorides are shown in Table IV.



(47)

TABLE IV

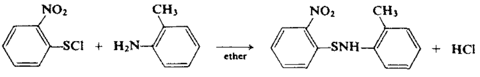
PREPARATION OF SULFENAMIDES BY THE REACTION OF *o*-NITROBENZENESULFENYL CHLORIDE (A)[a] OR 2,4-DINITROBENZENESULFENYL CHLORIDE (B)[b] WITH AMINE IN ETHER SOLUTION

| Sulfenyl chloride A or B | Amine | M.p. (°C) | Sulfenyl chloride A or B | Amine | M.p. (°C) |
|---|---|---|---|---|---|
| A | Ammonia | 124–125 | A | *α*-Naphthylamine | 130.5–131 |
| A | Aniline | 88.5–89 | B | *α*-Naphthylamine | 188.5–189 |
| | | (95)[c] | A | *β*-Naphthylamine | 202–202.5 |
| B | Aniline | 142.5–143 | B | *β*-Naphthylamine | 167–168 |
| A | *N*-Methylaniline | 86–86.5 | A | Methylamine | 35.5–36 |
| A | *p*-Anisidine | 138–138.5 | B | Methylamine | 99–99.5 |
| B | *p*-Anisidine | 158–159 | A | Ethylamine | 32.5–33 |
| A | *p*-Bromoaniline | 146–146.5 | B | Ethylamine | 66–66.5 |
| B | *p*-Bromoaniline | 180.5–181 | A | *n*-Propylamine | Oil |
| A | *p*-Chloroaniline | 143.5–144 | B | *n*-Propylamine | 94–94.5 |
| B | *p*-Chloroaniline | 164–164.5 | A | *n*-Butylamine | 27–28 |
| A | *o*-Toluidine | 115.5–116 | A | Dimethylamine | 62.5–63 |
| | | (119.5–120)[c] | A | Diethylamine | Oil |
| B | *o*-Toluidine | 115–156 | A | Cyclohexylamine | 51.5–52 |
| A | *p*-Toluidine | 136–136.5 | B | Cyclohexylamine | 109.5–110 |
| | | (135)[c] | B | *N*-Methylcyclohexylamine | 95.5–96 |
| B | *p*-Toluidine | 161–161.5 | | | |
| A | *m*-Toluidine | 106.5–107 | | | |

[a] J. H. Billman and E. O'Mahony, *J. Amer. Chem. Soc.* 61, 2340 (1939). [b] J. H. Billman, J. Garrison, R. Anderson, and B. Wolnak, *J. Amer. Chem. Soc.* 63, 1920 (1941). [c] M. L. Moore and T. B. Johnson, *J. Amer. Chem. Soc.* 57, 1517 (1935).

Sulfenyl halides such as tritylsulfenyl chloride and *o*-nitrophenylsulfenyl chloride also find use as nitrogen-protecting groups for amino acid esters [91a]. These groups show no steric hindrance and have been used to synthesize *N*-protected dipeptide esters. The *N*-sulfenyl group is easily cleaved by means of two equivalents of hydrogen chloride in methanol or nonpolar solvents with the reformation of the sulfenyl halide.

### *4-1. Preparation of* o-*Nitrophenylsulfen*-o-*toluidide* [92]

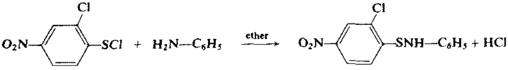


(48)

To a flask containing 50 gm (0.26 mole) of *o*-nitrophenylsulfenyl chloride dissolved in 500 ml of anhydrous ether is added dropwise 55 gm (0.51 mole) of *o*-toluidine dissolved in 50 ml of ether. The reaction is exothermic, and the solution refluxes during the addition. After 1 hr, the toluidine hydrochloride precipitate is filtered, washed with ether, and the combined ether solution concentrated under reduced pressure to afford 60 gm (89%) of an orange-red solid, m.p. 119.5–120°C.

Using a similar method the following sulfenamides were prepared: *o*-nitrophenylsulfenanilide, m.p. 95°C; *p*-nitrophenylsulfenanilide, m.p. *75°C; o-nitrophenylsulfen-p-toluidine, m.p. 135°C.*

### *4-2. Preparation of 2,4-Nitrochlorobenzenesulfenanilide* [91b]



(49)

To a flask containing 25 gm (0.11 mole) of 2,4-nitrochlorobenzenesulfenyl chloride dissolved in 500 ml of ether is added dropwise 23 gm (0.25 mole) of aniline dissolved in 50 ml of ether. The reaction is exothermic and is allowed to reflux during the dropwise addition of aniline. After 1 hr, the aniline hydrochloride is filtered, and the ether concentrated to afford 33 gm (98%) of a yellow-orange solid, m.p. 102°C (from ethanol).

The following other sulfenamides were prepared by a similar method: 2,4,-nitrochlorobenzenesulfen-*o*-toluidine, m.p. 127°C; 2-nitrobenzenesulfen-*o*-chloroaniline, m.p. 130°C; 4-nitrobenzenesulfen-*o*-chloroanilide, m.p. 99–101°C.

The use of the sulfenyl chloride route to sulfenamides has a number of disadvantages (both for the aromatic and aliphatic sulfenamides—see Section b). The chlorination of the disulfides leads to side reactions, particularly in the case of aliphatic disulfides, and the sulfenyl chlorides are also thermally unstable, easily hydrolyzed, and reactive with hydroxyl groups, methylene groups, and multiple bands [75b].

Another limitation to the preceding method is that by-product (trace amounts) of amine hydrochloride activates the S–N band toward attack by nucleophiles and therefore lowers the storage stability of the resulting sulfenamides [75b].

### b. THE USE OF ALKYL SULFENYL CHLORIDES

Heimer and Field [91c] recently described a variety of sulfenamides they prepared, starting with 2-acetamidoethanesulfenyl chloride. The sulfenamides were prepared by adding a cold methylene chloride solution of the sulfenyl chloride to the amine or amide in methylene chloride with triethylamine present as an acid scavenger. The results are summarized in Eq. 50 and Table V.

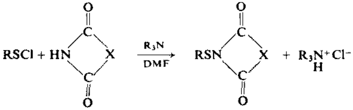
$$CH_3CONHCH_2CH_2SCl + RR'NH \xrightarrow[CH_2Cl_2]{Et_3N} CH_3CONHCH_2CH_2SNRR' + Et_3NHCl \qquad (50)$$

TABLE V

PREPARATION OF SULFENAMIDES BY THE REACTION SHOWN IN EQ. (50) [91c]

| RR'NH | | Yield | Physical properties |
|---|---|---|---|
| R = | R' = | (%) | of the sulfenamides |
| H | H | Low yields | — |
| H | $CH_2COOC_2H_5$ | Low yields | — |
| H | 1-Adamantane | 73 (crude) | — |
| H | $p$-$C_6H_4COOCH_3$ | 55 (crude) | m.p. 98°–100°C |
| H | 2-Benzothiazolyl | 63 | m.p. 140°–141°C |
| $C_2H_5$ | $C_2H_5$ | 39 (crude) | $n_D^{25}$ 1.4899 |
| $-(CH_2)_5-$ | | 51 (crude) | b.p. 80°C (0.08 mm Hg)<br>$n_D^{28}$ 1.5160 |
| $-(CH_2)_2O(CH_2)_2-$ | | 29 (crude) | $n_D^{28}$ 1.5150 |
| –$o$-phthaloyl– | | 45 | m.p. 144°–149°C |
| H | $p$-$CH_3C_6H_4SO_2$ | 64 | m.p. 120.5°–121°C |
| –succinimide– | | Low yields | — |

These results given in Table V indicate that strong basicity of the amine RR'NH in Eq. 50 affords purified products in low yields or that are thermally unstable at 25–60°C. Using diethylamine, piperidine, or morpholine gave products which were difficult to purify by short-parth distillation. Less basic aryl or heterocyclic amines afforded crystalline solids that were easily recrystallized. The less basic phthalimide also gave a sulfenamide that was easily purified by recrystallization (methanol). More recently, Behforouz and Kerwood [93] reported that other sulfenyl chlorides also react with imides in the presence of tertiary amines, to give alkyl or aryl sulfenamides derived from phthalimide, tetrahydrophthalimide, and succinimide, as shown in Eq. 51.

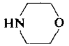


(51)

Other alkyl sulfenamides have been prepared by several methods and are summarized in Table VI.

TABLE VI

Preparation of Alkyl Sulfenamides ($RSNR'$ or $RSNR_2'$)

| RSX | | $R'NH_2$ or $R_2'NH$ | Yield (%) | B.p., °C (mm Hg) or m.p., °C | $n_D$ (°C) | Ref. |
|---|---|---|---|---|---|---|
| R= | X= | | | | | |
| $(CH_3)_3C$ | Cl |  | — | 50 (1) | 1.4745<br>(25) | *a* |
| $CCl_3$ | Cl | $ClCH_2SNHC_6H_5$ | — | 133–134 | — | *b* |
| $C_2H_5$ | SSCN | $(C_2H_5)_2NH$ | 31 | 61 (38) | 1.4500<br>(26) | *c* |
| $(CH_3)_3C$ | SSCN | $(n\text{-}C_4H_9)_2NH$ | 77 | 60–62<br>(0.67) | 1.4539–1.4542<br>(28) | *c* |

[a] C. M. Himel, U.S. Pat. 2,807,615 (1957). [b] J. R. Geigy, Swiss Pat. 317,878 (1957).
[c] R. T. Major and L. H. Peterson, *J. Amer. Chem. Soc.* **78**, *6181 (1956).*

## TABLE VII

### SULFENAMIDES FROM DISULFIDES

| Disulfide | Amine | Conditions | Product RSNHRR<br>% Yield | B.p.°C | M.p.°C | Ref. |
|---|---|---|---|---|---|---|
| *p*-Tolyl | Piperidine | $AgNO_3$-$CH_3OH$ | 60 | 78–79 (0.005) | — | [75*b*] |
| Phenyl | Diisopropyl amine | $AgNO_3$-$CH_3OH$ | 73 | 71–73 (0.4) | — | [75*c*] |
| 2-Benzothiazoyl | Isopropyl amine | $AgNO_3$-$CH_3OH$ | 90 | — | — | [75*e*] |
| 2-Benzothiazoyl | Piperidine | | 90 | — | — | [75*f*] |
| 2-Benzothiazoyl (Intermediate)[a] | Morpholine | NaOCl | 92 | 83–85 | 83–85 | [84*b*] |
| Methyl | Piperidine | AgOAc-EtOAc | 43 | 58(10) | — | [75*b*] |
| Ethyl | Piperidine | AgOAc-EtOAc | 30 | 37–38 (0.32) | — | [75*b*] |
| Benzyl | Diethylamine | AgOAc-EtOAc | 58 | 79–82 (0.07) | — | [75*b*] |

[a] Started with 2-Mercaptobenzothiazole.

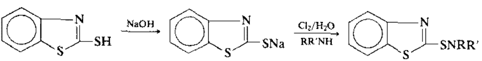
### C. The Preparation of Sulfenamides from Aromatic or Aliphatic Disulfides

The metal-assisted synthesis of sulfenamides from disulfides and amines (Eq. 52) offers an alternative approach to the preceding methods from the sulfenyl halides [75b].

$$\mathrm{RSSR + MX \xrightarrow{2R_2NH} RSNR_2 + RSM + R_2NH^+{}_2X^-} \qquad (53)$$

where R = alkyl, aryl; MX = $AgNO_3$, AgOAc, $HgCl_2$.

The disulfide can also be an intermediate in the oxidative condensation of thiols with amines, as in the case of 2-mercaptobenzothiazole (MBT) [84b]. See Table VII for additional examples.



(54)

The electrolytic coupling of 2-mercaptobenzothiazole disulfide or an alkali metal salt of MBT in the presence of amines (primary or secondary) gives the sulfenamide [75g].

## 5. SULFENATES

Sulfenates, RSOR, are the sulfur analogs of the peroxides; however, they are stable enough to be used as derivatives to characterize alcohols [94–96]. In most cases, they can be recrystallized without undergoing decomposition. At elevated temperatures, sulfenates decompose, and some decompose at the melting point (*t*-butyl-2,4-dinitrobenzenesulfenate decomposes at the m.p. 118–119°C).

Benzylic trichloromethane sulfenates have been reported to thermally rearrange to sulfoxides [96c]. This is also true for other benzyl sulfenates [96d].

Sulfenates are rarely prepared by the direct [9] reaction of sulfenic acids with alcohols because the former are difficult to prepare. Sulfenates are more commonly prepared by the reaction of sulfenyl halides with sodium alkoxides or phenoxides [10c,e,f, 12a, 13a, 61, 66, 97] or the reaction of the sulfenyl halides with the alcohol in the presence of a tertiary amine [94–96].

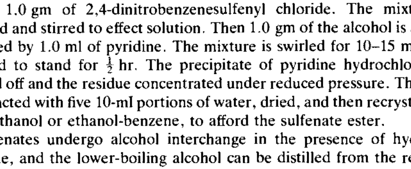
Sulfenates are conveniently prepared by the reaction of sulfenyl halides with alcohols in the presence of pyridine, to give the sulfenates in 80–95% yields [94–98]. Sulfenates prepared from 2,4-dinitrobenzenesulfenyl chloride are solids, and in some cases, they decompose at the melting point, as seen in Tables VIII and IX. The presence of pyridine is not essential but the reaction is faster and goes to completion, giving little of the disulfide by-product [94–96].

The sulfenate esters have been reported to be pesticidally active and useful as preemergent herbicides. For example, $C_6H_5\text{-}SO_2CCl_2SOCH_3$, m.p. 71–79°C) has been described in a patent for this application [96b].

### *5-1. General Procedure for the Preparation of Sulfenates Described in Tables VIII and IX*

To a 50-ml Erlenmeyer flask containing 10 ml of ethylene dichloride is added 1.0 gm of 2,4-dinitrobenzenesulfenyl chloride. The mixture is warmed and stirred to effect solution. Then 1.0 gm of the alcohol is added, followed by 1.0 ml of pyridine. The mixture is swirled for 10–15 min and allowed to stand for $\frac{1}{2}$ hr. The precipitate of pyridine hydrochloride is filtered off and the residue concentrated under reduced pressure. The solid is extracted with five 10-ml portions of water, dried, and then recrystallized from ethanol or ethanol-benzene, to afford the sulfenate ester.

Sulfenates undergo alcohol interchange in the presence of hydrogen chloride, and the lower-boiling alcohol can be distilled from the reaction mixture [94].



$$2,4\text{-}(NO_2)_2C_6H_3SCl + \underset{O}{CH_2\text{—}CH_2} \xrightarrow[\underset{Cl\quad Cl}{CH_2\text{—}CH_2}]{\text{pyridine}} 2,4\text{-}(NO_2)_2C_6H_3SOCH_2CH_2Cl \qquad (54)$$

50%

m.p. 120°–121°C

Sulfenates can also be prepared by the reaction of sulfenyl halide with epoxides catalyzed by pyridine, to give chloroalkyl sulfenates as described in Eq. (54) and Table X.

Few sulfenates are known in which R and R′ of RSOR′ are both aliphatic [23a, 61, 99]. Recently, several alkyl sulfenates were prepared by Moore and O'Connor [100] by the reaction of lithium alkoxides with sulfenyl chlorides in an organic solvent. Table XI summarizes the experimental details of three representative preparations. The sulfenates are easily oxidized by air and most oxidizing agents, to afford high yields of sulfinate esters.

## TABLE VIII

### REACTION OF 2,4-DINITROBENZENESULFENYL CHLORIDE WITH ALCOHOLS

| Alcohol | Alkyl 2,4-dinitrobenzene-sulfenate; Ar = 2,4-dinitrophenyl | *Yield*[a] (%) | *M.p.*[b] (°C) | Alcohol | Alkyl 2,4-dinitrobenzene-sulfenate; Ar = 2,4-dinitrophenyl | *Yield*[a] (%) | *M.p.*[b] (°C) |
|---|---|---|---|---|---|---|---|
| Methyl[c] | $ArSOCH_3$ | 95 | 122–123 | Isoamyl | ArSO-*i*-$C_5H_{11}$ | 85 | 56–57 |
| Ethyl[c] | $ArSOC_2H_5$ | 85 | 124–125 | *t*-Amyl | ArSO-*t*-$C_5H_{11}$ | 85 | 102–103 |
| *n*-Propyl | ArSO-*n*-$C_3H_7$ | 85 | 75–76 | *n*-Octyl | ArSO-*n*-$C_8H_{17}$ | 90 | 57–58 |
| Isopropyl | ArSO-*i*-$C_3H_7$ | 90 | 77–78 | Lauryl | ArSO-*n*-$C_{12}H_{25}$ | 85 | 73–74 |
| *n*-Butyl | ArSO-*n*-$C_4H_{10}$ | 85 | 53–54 | Cyclohexanol | ArSO-cyclo-$C_6H_{11}$[d] | 85 | 133–134 |
| *s*-Butyl | ArSO-*sec*-$C_4H_{10}$ | 80 | 71–72 | Cholesterol | $ArSOC_{27}H_{45}$[d] | 80 | 189–190 |
| *t*-Butyl | ArSO-*t*-$C_4C_{10}$ | 80 | 118–119 | *l*-Menthol | $ArSOC_{10}H_{16}$ | 85 | 99–100[g] |
| *n*-Amyl | ArSO-*n*-$C_5H_{11}$ | 85 | 31–32[f] | Benzyl | $ArSOCH_2C_6H_5$[d,e] | 95 | 142–143 |

[a] Yields listed are for the crude, dry products, based on amount of sulfenyl chloride (I) used. Since some of I was generally converted to insoluble residue, $R_1$, the stated yields would be increased somewhat if this were taken into account. Losses of 10–15% were usually incurred in recrystallizations to products melting within 2°–3°C (and often within only 1°) of the melting points recorded for the analytical samples. All of the above products were obtained by the general procedure, using pyridine.

[b] Melting points were made on a Fisher–Johns apparatus. Mixed-melting points between the methyl and ethyl derivatives, and the *n*-propyl and isopropyl compounds gave sharp depressions. Melting of the *t*-butyl derivative was accompanied by evolution of a gas.

[c] The methyl and ethyl esters were reported previously.

[d] These products were best recrystallized from approximately equal volumes of absolute alcohol and benzene. The other products were all recrystallized from absolute alcohol.

[e] Decomposition to tars was sometimes noted in this case if the product was not carefully washed and recrystallized.

[f] The product in this case was an oil which crystallized only with some difficulty.

[g] In these cases, a colorless, crystalline, hygroscopic precipitate (probably pyridine–hydrochloride) formed on adding the pyridine to the solution in ethylene chloride. While the identity of this product was not established, it was water soluble, and did not interfere with the isolation of the sulfenate esters.

[Adapted from N. Kharasch, D. P. McQuarrie, and C. M. Buess, *J. Amer. Chem. Soc.* **75**, 2658 (1953). Copyright 1953 by the American Chemical Society. Reprinted by permission of the copyright owner.]

## TABLE IX

### SULFENATE ESTERS (THIOPEROXIDES) OBTAINED WITH 2,4-DINITROBENZENESULFENYL CHLORIDE (I)

| Alcohol | Type of product (Ar = 2,4-dinitrophenyl) | Yield (%) | M.p. (°C) | Alcohol | Type of product (Ar = 2,4-dinitrophenyl) | Yield (%) | M.p. (°C) |
|---|---|---|---|---|---|---|---|
| Allyl | Ester, ArSOR<br>$C_9H_8N_2O_5S$ | 14[e] | 86–87 | Pinacol | Diester[d]<br>$C_{18}H_{18}N_4O_{10}S_2$ | 33[h] | 133.5–135 (dec.) |
| Cinnamyl | Ester<br>$C_{15}H_{12}N_2O_5S$ | 35[f] | 120–123 (dec.)[a] | α-Phenylethanol | Ester<br>$C_{14}H_{12}N_2O_5S$ | 93 | 92–93[b] |
| Ethylene glycol | Monoester<br>$C_8H_6N_2O_6S$ | 75[g] | 113.5–114 | 2-Methyl-3-butyn-2-ol[i] | Ester<br>$C_{11}H_{10}N_2O_5S$ | 80 | 96–97 |
| Ethylene glycol | Diester<br>$C_{14}H_{10}N_4O_{10}S_2$ | 91 | 170–171.5 (dec.) | Benzhydrol | Ester<br>$C_{19}H_{14}N_2O_5S$ | 29[j] | 113 dec[c] |
| | | | | Triphenylcarbinol | —[k] | — | — |

[a] This melting point depends considerably on the rate of heating and temperature of introduction of the sample. [b] The melting point of once-recrystallized sample was 95°–96°C; further recrystallizations lowered the melting point. [c] This compound melts indefinitely and the melting point drops sharply on recrystallization. The poor analytical figures undoubtedly reflect its instability. [d] *Anal.* Calcd.: S, 12.46; N, 10.89. Found: S, 12.60; N, 10.67. [e] The other product was a viscous yellow oil (44%). *Anal.* Calcd. for $C_9N_9N_2O_5SCl$: C, 36.93; H, 3.10; N, 9.57; Cl, 12.11. Found: C, 37.11; H, 2.97; N, 9.79; Cl, 12.02. [f] A dark brown, amorphous residue was obtained in this reaction if pyridine was absent. The yield of this, calculated for the 1:1 adduct, was quantitative. *Anal.* Calcd. for the 1:1 adduct of cinnamyl alcohol and I, $C_{15}H_{13}N_2O_5SCl$: C, 48.85; H, 3.55; N, 7.59. Found: C, 48.52; H, 3.84; N, 7.39. [g] The diester, $C_{14}H_{10}N_4O_{10}S_2$ (20% yield), dec. 170°–171.5°C, was also found. [h] Also a 33% yield of 2,4-dinitrophenylsulfide. [i] Kindly supplied by Air Reduction Corporation. Propargyl alcohol (gift of General Aniline and Film Corporation) failed to give any ester; *cf.* discussion. With 2-methyl-3-butyn-2-ol, two crystalline forms of the ester were noted when the crude product (melting partially at 87°, but mainly at 93°–97°C) was recrystallized from ligroin (b.p. 63°–69°C): needles, m.p. 87.5°–89.5°C, and more massive crystals, m.p. 96.2°–98°C. Both crystal forms are interlocked in the product and difficult to separate. The analysis recorded was made on a crystal melting at 96°–97°C. A sample which showed melting at 87.5°–89.5°C and 95.5°–97.5°C (mixture of both forms) gave: C, 47.90; H, 3.83; N, 10.27. [j] $(ArS)_2$ (39%) and some crude pyridinum 2,4-dinitrobenzenesulfonate also were found. The sulfonic acid no doubt arises by hydrolysis of I as found by N. Kharasch, W. King, and T. C. Bruice, *J. Amer. Chem. Soc.* 77, 931 (1955). [k] No ester could be obtained. Products included: crude triphenylmethyl chloride (trace); pyridinium 2,4-dinitrobenzenesulfonate (m.p. 196°–199°C), after recrystallization from ethylene chloride, and not depressing the m.p. of the salt prepared from the sulfonic acid (obtained by oxidizing I with nitric acid) and pyridine. *Cf.* also footnote above. *Anal.* Calcd. for pyridinium 2,4-dinitrobenzenesulfonate, $C_{11}H_9N_3O_7S$: C, 40.37; H, 2.77; N, 12.87; S, 9.82. Found: C, 40.51; H, 2.83; N, 12.82; S, 8.97. Unchanged triphenylcarbinol (m.p. 159°–132°C) also was found in considerable amount. [Adapted from L. Goodman and N. Kharasch, *J. Amer. Chem. Soc.* 77, 6541 (1955). Copyright 1955 by the American Chemical Society. Reprinted by permission of the copyright owner.]

### TABLE X

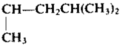
PREPARATION OF CHLOROALKYL SULFENATES BY THE REACTION OF EPOXIDES WITH SULFENYL CHLORIDES[a]

| RSCl | Epoxide | Yield (%) | B.p., °C (mm Hg) or m.p., °C | $n_D^{20}$ |
|---|---|---|---|---|
| $2,4(O_2N)_2C_6H_3$– | Ethylene oxide | 50 | 120–121 | — |
| $2,4(O_2N)_2C_6H_3$– | Cyclohexene oxide | 78 | 140–145 dec. | — |
| $2,4(O_2N)_2C_6H_3$– | Propylene oxide | 30 | 106–107 | — |
| $2,4(O_2N)_2C_6H_3$– | *cis*- or *trans*-Stilbene oxide | 0 | — | — |
| $CCl_3SCl$ | Ethylene oxide | 85 | 45–46<br>(0.15) | 1.5233 |
| $CCl_3SCl$ | Propylene oxide | 81 | 49.5–50.5<br>(0.15) | 1.5122 |
| $CCl_3SCl$ | 3-Chloropropylene oxide | 76 | 75–76<br>(0.2) | 1.5321 |
| $CCl_3SCl$ | Styrene oxide | 74 | 119–121<br>(0.12) | 1.5720 |
| $CCl_3SCl$ | Mixed butene oxides | 84 | 51–52<br>(0.15) | 1.5720 |

[a] N. Kharasch and R. B. Langford, U.S. Pat. 2,929,824 (1960); *Chem. Abstr.* **54**, 13064 (1960).

### TABLE XI

PREPARATION OF ALKYL SULFENATES, $CH_3SOR'$ [100]

| RSCl (moles), R = | R′OLi (moles), R′ = | Solvent 1,2-Dimethoxyethane (ml) | Reaction conditions Temp. (°C) | Time (hr) | Yield (%) | B.p., °C (mm Hg) |
|---|---|---|---|---|---|---|
| $CH_3$<br>(0.2) | $C_5H_{11}$<br>(0.4) | 200 | −30 to −60 | ½–1 | 74 | 57–58<br>(15) |
| $CH_3$<br>(0.2) |  $CH(CH_3)$—$CH_2CH(CH_3)_2$<br>(0.2) | 100 | −40 to −50 | ½–1 | 48 | 57.5<br>(17) |
| $CH_3$<br>(0.2) | $C(CH_3)_3$<br>(0.2) | 100 | −40 to −60 | ½–1 | 45 | 53<br>(75) |

It has been briefly reported that the reaction of mercaptides with alkyl hypochlorites affords not the sulfenates, but the disulfides (Eq. 55) [101]. A further investigation of this reaction may be worthwhile.

$$\mathrm{R'SOR} \;\not\longleftarrow\; \mathrm{ROCl + 2R'SNa} \longrightarrow \mathrm{RONa + R'SSR' + NaCl} \tag{55}$$

## 6. MISCELLANEOUS METHODS

(1) Sulfenyl bromides from sulfinic acids [102].

(2) Preparation of *t*-butyl sulfenyl chloride by the reaction of sodium hypochlorite with *t*-butyl mercaptan [103].

(3) Preparation of benzenesulfenyl chloride by the reaction of hydrogen chloride with benzenesulfenodiethylamide in absolute ether as solvent [56].

(4) Preparation of sulfenyl chloride by the reaction of sulfenamides with hydrogen chloride [87, 88].

(5) Preparation of sulfenyl halides by the reaction of hydrogen halide with sulfenic esters [14].

(6) Preparation of sulfenyl chlorides by the reaction of phosphorus pentachloride with sulfenic anhydrides [14].

(7) Preparation of sulfenyl bromide by the reaction of sulfenamides with hydrogen bromide [87, 88].

(8) Preparation of tetra-*o*-acetylglycosylsulfenyl bromide [104].

(9) Preparation of sulfenyl chlorides by the chlorination of thiocyanates [105].

(10) Preparation of 3-chloroformylpropanesulfenyl chloride [106].

(11) Preparation of aliphatic and aromatic sulfenyl halides by the reaction of the corresponding mercaptan or thiol with *N*-chloro- or *N*-bromosuccinimide [107].

(12) Preparation of sulfenyl thiocyanates by the reaction of a sulfenyl halide with a metal thiocyanate [108].

(13) Preparation of sulfenyl thiocyanate by the reaction of a thiophenol or mercaptan with thiocyanogen [38].

(14) Displacement of amino groups of sulfenamides by reaction with amines whose base strength is greater. For example, reaction of 2-benzothiazole-sulfenamide with cyclohexylamine to give 2-benzothiazole-sulfenocyclohexyl-amide and ammonia [109].

(15) Preparation of benzenediazo triphenylmethyl sulfide from the reaction of benzenediazonium chloride and triphenylmethylthiol [110].

(16) Preparation of *N*-benzylidene-4-chloro-2-nitrobenzenesulfenamide

by the reaction of 4-chloro-2-acetobenzenesulfenamide and benzaldehyde in boiling ethanol [12a].

(17) Preparation of *S*-aryl thiosulfates ($C_6H_5—S—SO_3^-$) (aryl Bunte salts) [11].

(18) Preparation of sulfenic anhydride (thiosulfinates) (RSOSR) [12a, 112].

(19) Preparation of sulfenyl carboxylates ($\mathrm{RSO\overset{\overset{O}{\|}}{C}R}$) [113].

(20) Preparation of sulfenyl nitrates ($RSONO_2$) [114].

(21) Preparation of salts of aromatic sulfenic acids by the reaction of aromatic thiosulfinic acid esters with Grignard reagents [115].

(22) Preparation of sulfenic acids by the thermal decomposition of sulfoxides [116].

(23) Preparation of sulfenamides by the copper-catalyzed reaction of azide with thiols [117].

(24) Preparation of sulfilimines and sulfenamides from *N*-chlorobenzimidates and sulfur nucleophiles [118].

(25) Preparation of sulfenyl nitrates [114].

(26) Preparation of aminecarbotrithioates by the reaction of carbon disulfide with sulfenamides [119].

(27) Exchange reaction of arenesulfenyl chlorides with organic disulfides [120].

(28) Trapping of sulfenic acids from penicillin sulfoxides [121].

(29) Preparation of *N*-trichloromethylsulfenyl arenesulfonyl arylamides [122].

(30) Preparation of $\alpha,\alpha$-dichlorosulfenyl chlorides by the reaction of *S*-benzylsulfides containing an active methylene group with sulfenyl chlorides [123].

(31) Preparation of 1,2,4-thiadiazolylsulfenyl chloride [124].

(32) Sulfenamides derived from *N*-chlorobenzimidates [125].

(33) Preparation of aminosulfenyl chlorides [126].

(34) Preparation of trichloromethylsulfenylsulfonyldichloromethane [127].

(35) Preparation of acetylsulfenyl chloride [128].

(36) Preparation of sulfenamides from thiopthalimides [129].

(37) Preparation of $\alpha$-(carbamoyl)-$\alpha,\alpha$-dichloromethylsulfenyl chloride by a two-step synthesis [130].

(38) Preparation of sulfenimines (*S*-Arylthiooximes) [131].

(39) Preparation of alkyl thio/sulfinate esters [132].

(40) $\beta$-Lactam sulfenic acid derivatives [133].

(41) Azetidinone sulfenic acids [134].

(42) Preparation of trichloromethanethiosulfenyl chloride ($CCl_3SSCl$) [135].

(43) Preparation of 2,6-dialkyl-4-hydroxyphenyl-sulfenyl chloride by reaction of sulfur monochloride with 3,5-dialkylphenol [136].

(44) Preparation of amido-methanesulfenyl chlorides [137].

(45) Preparation of oxamoylsulfenyl chlorides [138].

(46) Preparation of *N*-substituted acylamidosulfenyl chlorides [139].

(47) Preparation of methyl (*N*-2-4-xylyformamidoyl) amido-sulfenyl chloride [140].

(48) Preparation of aminosulfenyl chloride and derivatives [141].

(49) Preparation of substituted thiazole sulfenamides [142].

(50) Preparation of sulfenic acids from *N*-alkylidenearenesulfinamides (sulfinimines) [143].

(51) Trialkylamine/sulfur dioxide catalyzed sulfenylation of carbamates [144].

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In contrast to the nitriles, the isonitriles have a highly disagreeable odor, which is valuable in detecting their presence. In fact, some of the routes to their formation were discovered by the resulting odor of the reaction mixture.

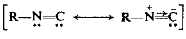
The structure of the isonitriles differs from that of the nitriles (I), as shown in (II).

$R{-}C{\equiv}N$
Nitriles

(I)

$R{-}N\overset{\rightarrow}{=}C$
Isonitriles

(II)



$$\left[R{-}\underset{\cdot\cdot}{N}{=}\underset{\cdot\cdot}{C} \longleftrightarrow R{-}\overset{+}{N}\overset{\rightarrow}{=}\underset{\cdot\cdot}{\overset{-}{C}}\right]$$

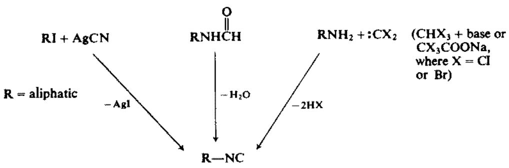
Some of the most important methods of preparing isonitriles are shown in Scheme 1.

Formerly, isonitriles had found only limited laboratory and industrial use because of preparative limitations. As is discussed later, the ease of dehydration of formamides has prompted renewed interest in the use of this functional group in insecticides [4a–e], acaricides [4a–e], and fungicides [4a–e]; as cross-linking agents for carboxyl-containing polymers [5]; in synthesis of imidazolidines [6], indoles [7], and isocyanates [8a–c]; and in the preparation of novel polymers [9a–c]. In addition, two reviews [10a–b] and a monograph [11] on isonitriles have appeared. The chemistry of the related nitriles has been described in Volume I of this series [12].

Although several reports indicate very low toxicity of isonitriles toward mammals, great caution should be exercised because butane 1,4-diisonitrile (1,4-diisocyanobutane) has been found extremely toxic (LD$_{50}$, mice $< 10$ mg/kg) [13]. The extremely disagreeable odor of isonitriles, which can be detected in minute amounts, has fortunately served to alert investigators of their presence.

Adequate shielding should be used in heating all isonitriles because explosions have been reported where ethyl isonitrile [14] and isocyanoethyl

SCHEME 1
Preparation of Isonitriles



# CHAPTER 5/ISONITRILES (ISOCYANIDES)

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## 1. INTRODUCTION

Isonitriles were first synthesized by Lieke [1] and then by Meyer [2], but these early investigators erroneously assumed they had nitriles. Gautier [3a–i] was the first to recognize the isonitrile structure and to describe a general synthesis of many of these compounds from the reaction of silver cyanide with alkyl iodides (Eqs. 1–3).

$$CH_2{=}CH{-}CH_2I + AgCN \xrightarrow{[1]} CH_2{=}CH{-}CH_2NC + AgI \qquad (1)$$

$$CH_3I + AgCN \xrightarrow{[2]} CH_3NC + AgI \qquad (2)$$

$$CH_3CH_2I + AgCN \xrightarrow{[2]} CH_3CH_2NC + AgI \qquad (3)$$

benzenesulfonate [15a] have been heated in the absence of solvents. In most other cases, no explosions have been reported where distillations were carried out at reduced pressures with mild heating.

Isonitriles have also been named isocyanides, but the former is used in *Chemical Abstracts* and is used in this chapter.

Recently, it has been reported that isonitriles undergo a thermal rearrangement to the nitrile.

$$\text{R—NC} \longrightarrow \text{R—CN}$$

The isonitrile–nitrile rearrangement is a noncatalytic, high-yielding unimolecular thermal-gas-phase reaction.

*Trans*-2-butenyl isonitrile was reported to be isomerized by vacuum flash thermolysis to *trans*-2-butenyl nitrile without detectable allylic rearrangement.

$$\textit{trans}\text{-}CH_3CH{=}CH{-}CH_2NC \longrightarrow \underset{(98\%\ \text{yield})}{\textit{trans}\text{-}CH_3CH{=}CH{-}CH_2CN} \qquad (5)$$

The chemistry of isonitriles has also been earlier reviewed and is worthwhile consulting [15b].

In a similar fashion (and yield), the following isonitriles were isomerized [15c,d].

$$1\text{-}C_8H_{17}NC \longrightarrow 1\text{-}C_8H_{17}CN \qquad (6)$$

$$C_6H_5CH_2NC \longrightarrow C_6H_5CH_2CN \qquad (7)$$

$$2,4,6\text{-}(CH_3)_3C_6H_2{-}NC \longrightarrow 2,4,6\text{-}(CH_3)_3C_6H_2CN \qquad (8)$$

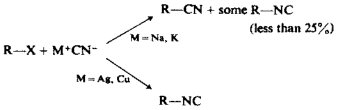
## 2. CONDENSATION REACTIONS

The two most important condensation reactions to afford isonitriles are (a) the alkylation of cyanides and (b) the reaction of dihalocarbenes with primary amines under strongly basic conditions. These reactions usually give lower yields of isonitriles than those obtained by the dehydration of formamides. Of course, the choice of methods depends on the availability of the particular starting material. However, because primary amines are readily converted to the formamide, the dehydration method should still be used where possible.

### A. Reaction of Active Halides and Olefins with Cyanides

Free cyanide ion [16] reacts with either alkyl halides, alkali monoalkyl sulfates, or dialkyl sulfates, to afford mainly nitriles with approximately less than 25% of the isonitrile (Eq. 4) [17a,b]. The use of some heavy metal cyanides reacts more favorably and affords mainly isonitriles. Thus, for example, Ag [18a] and Cu(I) are effective, whereas Zn, Cd, and Ni afford poor yields of isonitriles [18b].

The reaction has the advantage that reactive alkyl or aryl halides may be converted to isonitriles. Although the reaction has been mainly carried out with silver cyanide, further work remains to be done to apply this reaction to less costly cyanide reagents to prepare isonitriles in almost quantitative yields.



(9)

$X = I, RSO_3, KSO_3$
R = alkyl groups

It should be noted that the reaction of aryl bromides with cuprous cyanide in DMF (dimethylformamide) has also been reported to give aryl cyanides [18c].

### *2-1. Preparation of Ethyl Isonitrile* [19, 20]

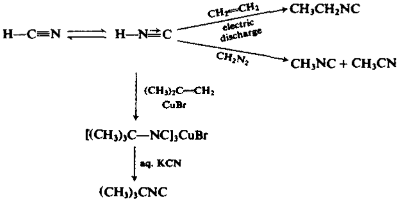
$$C_2H_5I + AgCN \longrightarrow [AgI—C_2H_5NC] \xrightarrow{2KCN} C_2H_5NC + KI + KAg(CN)_2 \quad (10)$$

**CAUTION:** The reaction and distillation should be conducted behind a safety shield. Precautions for handling toxic cyanides should be observed.

To a three-necked flask equipped with a condenser and ground glass stirrer (or Hershberg stirrer) is added 116 gm (0.75 mole) of ethyl iodide and 100 gm (0.75 mole) of silver cyanide. The mixture is refluxed for 2 hr, the stirrer blade raised, the mixture cooled, filtered (see Note a), the solid washed with ether, dried, and 260 gm of a 50% solution of potassium cyanide (2.0 moles) added. The reaction mixture is distilled to afford a mixture of isonitrile and water (see Note b). The crude isonitrile 49.5–52.3 gm (90–95%) is separated after being salted out of the water. The isonitrile is washed twice with 24-ml portions of ice-cold saturated sodium chloride solution, dried over magnesium sulfate, and fractionally distilled, to afford 25.9–30.3 gm (47–55%), b.p. 77–79°C (760 mm Hg); $n_D^{20}$ 1.3632.

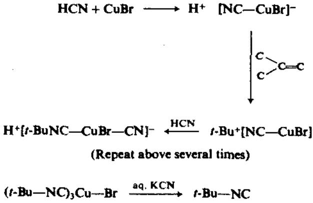
NOTES: (a) Filtration may be omitted and the aqueous potassium cyanide directly added to the product at this point. (b) The remaining aqueous potassium-cyanide–silver-cyanide solution should not be poured down the drain but put into special waste containers.

Hydrogen cyanide, which is tautomeric with hydrogen isonitrile [21a,b], reacts with diazomethane to afford a mixture of acetonitrile and methyl isonitrile [22]. Hydrogen cyanide also adds to ethylene under the action of a silent electric discharge to yield ethyl isonitrile [23a,b,]. However, hydrogen cyanide may also be added to olefins such as isobutene in the presence of cuprous halides to afford *t*-butyl isonitrile cuprous complexes. The addition of aqueous potassium cyanide yields the free *t*-butyl isonitrile [24a,b,c]. The reaction is illustrated in Eq. 6, and several examples are given in Table I.



(11)

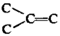
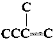
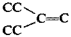
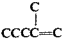
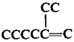
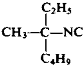
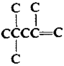
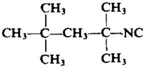
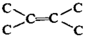
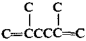
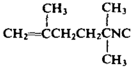
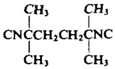
It should be noted that the gas-phase reaction of hydrogen cyanide [12] with branched-chain olefins over alumina [25], cobalt cyanide on alumina [26], or cobalt on alumina affords nitriles [12, 25]. Even the liquid-phase reaction of ethylene, propylene, and other α-olefins with hydrogen cyanide using catalytic amounts of dicobalt octacarbonyl affords nitriles [27a,b]. Therefore, the use of cuprous bromide must change the course of the reaction to afford isonitriles by alkylation of the cyanide ion on the nitrogen atom instead of the carbon atom. A tentative explanation proposed by Otsuka et al. [24] is shown in Eq. 12.



(12)

## TABLE I

OLEFINS AND ALKYL ISOCYANIDES OBTAINED BY THE NEW ALKYLATION REACTION

| Olefin | Isocyanide | Yield (moles/gm-atom of Cu) | B.p., °C (mm Hg) | $n_D^{20}$ |
|---|---|---|---|---|
|  | $(CH_3)_3CNC$ | 1.2 | 60–63 (314) | 1.3749 |
|  $CC\overset{\overset{C}{\vert}}{C}{=}C$ | $(CH_3)_2(C_2H_5)CNC$ | 1.6 | 68–69 (153) | 1.3938 |
|  | $(CH_3)(C_2H_5)_2CNC$ | 1.5 | 80–81 (100) | 1.4079 |
|  $CCC\overset{\overset{C}{\vert}}{C}{=}C$ | $(CH_3)_2(C_3H_7)CNC$ | 1.2 | 74–75 (92) | 1.4012 |
|  $CCCC\overset{\overset{CC}{\vert}}{C}{=}C$ |  $CH_3{-}\underset{\underset{C_4H_9}{\vert}}{\overset{\overset{C_2H_5}{\vert}}{C}}{-}NC$ | 1.7 | 103–104 (59) | 1.4210 |
|  $C\underset{\underset{C}{\vert}}{\overset{\overset{C}{\vert}}{C}}\overset{\overset{C}{\vert}}{C}{=}C$ |  $CH_3{-}\underset{\underset{CH_3}{\vert}}{\overset{\overset{CH_3}{\vert}}{C}}{-}CH_3{-}\underset{\underset{CH_3}{\vert}}{\overset{\overset{CH_3}{\vert}}{C}}{-}NC$ | 1.0 | 96–97 (69) | 1.4212 |
|  | $(CH_3)_2(i\text{-}C_3H_7)CNC$ | 1.1 | 73–75 (98) | 1.4072 |
|  $C{=}\overset{\overset{C}{\vert}}{C}CC\overset{\overset{C}{\vert}}{C}{=}C$ |  $CH_2{=}\overset{\overset{CH_3}{\vert}}{C}CH_2CH_2\underset{\underset{CH_3}{\vert}}{\overset{\overset{CH_3}{\vert}}{C}}NC$ | 0.88 | 95–97 (44) | 1.4365 |
| |  $CN\underset{\underset{CH_3}{\vert}}{\overset{\overset{CH_3}{\vert}}{C}}CH_2CH_2\underset{\underset{CH_3}{\vert}}{\overset{\overset{CH_3}{\vert}}{C}}NC$ | 0.17 | m.p. 125–126 | — |

[a] (Reprinted in part from S. Otsuka, K. Mori, and K. Yamagami, *J. Org. Chem.* **31**, 4170 (1966). Copyright 1966 by the American Chemical Society. Reprinted by permission of the copyright owner).

TABLE II

PREPARATION OF ISONITRILES BY THE REACTION OF DIHALOCARBENES WITH PRIMARY AMINES

| Amine, $RNH_2$ (moles) R = | $CHX_3$ (moles) | $CCl_3COONa$ (moles) | Base (moles) | Solvent (ml) | Reaction conditions: Temp. (°C) | Reaction conditions: Time (hr) | Isonitrile product: Yield (%) | Isonitrile product: B.p., °C (mm Hg) or m.p., °C | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| $C_6H_5$<br>(0.1) | X = Br<br>0.105 | — | NaH<br>0.33 | THF | ? | ? | 45 | 52–53 (13) | *a* |
| (0.2) | X = Cl<br>0.2 | — | KO-*t*-Bu<br>0.6 | Hexane | 0–5<br>25 | ½<br>4½ | 73 | — | *b* |
| *o*-$CH_3C_6H_4$<br>(0.2) | 0.2 | — | 0.6 | Hexane | 0–5<br>25 | ½<br>4½ | 71 | — | *b* |
| *p*-$CH_3C_6H_4$<br>(0.2) | 0.2 | — | 0.6 | Hexane | 0–5<br>25 | ½<br>4½ | 86 | — | *b* |
| *o*-$ClC_6H_4$<br>(0.2) | 0.2 | — | 0.6 | Hexane | 0–5<br>25 | ½<br>4½ | 93 | — | *b* |
| *p*-$ClC_6H_4$<br>(0.2) | 0.2 | — | 0.6 | Hexane | 0–5<br>25 | ½<br>4½ | 94 | — | *b* |
| $(C_2H_5)_2NCH_2CH_2CH_2$<br>(0.14) | 0.37 | — | KOH<br>0.72 | $C_6H_6$<br>100 | 80–90 | — | 20.5 | 105–107 (45) | *c* |
| $(CH_3)_2NCH_2CH_2CH_2$<br>(0.17) | 0.37 | — | 0.72 | 100 | 80–90 | — | 11 | 86–88 (55) | *c* |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| $(C_2H_5)_2NCH_2CH_2$<br>(0.18) | 0.50 | — | 1.0 | 140 | 80–90 | — | 14.8 | 94–95 (45) | *c* |
| $HOC(=O)-C_6H_4$<br>(0.23) | 0.42 | — | $\frac{\text{NaOH}}{0.75}$ | $\frac{CH_3OH}{100}$ | 66 | 2 | 34 | >300 | *d* |
| $C_6H_5$<br>(0.05) | — | 0.05 | — | $\frac{\text{1,2-Dimethoxy ethane}}{50}$ | 85 | 15 | 20 | 43–44 (1.5) | *e* |
| *p*-$ClC_6H_4$<br>(0.05) | — | 0.09 | — | 50 | 85 | 3/4 | Product not isolated | | *e* |
| *p*-$CH_3C_6H_4$<br>(0.05) | — | 0.15 | — | 100 | 85 | 1 | 43 | 38 (1)<br>19–20 | *e* |
| *p*-$CH_3OC_6H_4$<br>(0.05) | — | 0.16 | — | 100 | 85 | 1/2 | 38 | 45 (1)<br>28–30 | *e* |

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[a] H. W. Johnson, Jr., and H. Krutzsch, *J. Org. Chem.* **32**, 1939 (1967).

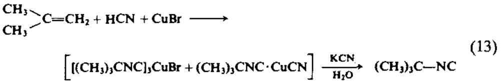
[b] T. Shingaki and M. Takebayashi, *Bull. Chem. Soc. Japan* 36(5), 617 (1963).

[c] P. A. S. Smith and N. W. Kalenda, *J. Org. Chem.* **23**, 1599 (1958).

[d] D. Samuel, B. Weinraub, and D. Ginsburg, *J. Org. Chem.* **21**, 376 (1956).

[e] A. P. Krapcho, *J. Org. Chem.* **27**, 1089 (1962).

### *2-2. Preparation of* t*-Butyl Isonitrile* [24]



$$(CH_3)_2C{=}CH_2 + HCN + CuBr \longrightarrow \Big[[(CH_3)_3CNC]_3CuBr + (CH_3)_3CNC\cdot CuCN\Big] \xrightarrow[H_2O]{KCN} (CH_3)_3C{-}NC \quad (13)$$

**CAUTION:** Use a well-ventilated hood and observe all precautions when using hydrogen cyanide.

To a 1-l, stainless steel Hoke pressure cylinder in a well-ventilated hood is added 196 gm (3.5 moles) of isobutene, 95 gm (3.5 moles) of hydrogen cyanide, and 100 gm (0.7 mole) or cuprous bromide. The cylinder is closed, shaken for 15 hr at 70°C, cooled to room temperature, and vented cautiously in the hood, and the viscous residue is poured slowly into aqueous potassium cyanide (260 gm in 100 ml of water) to decompose the cuprous complex, liberating an organic layer. The organic layer is separated, dried, and distilled under reduced pressure to afford 97 gm, b.p. 60–63°C (314 mm Hg), $n_D^{20}$ 1.3749, IR 2143 s, 1472 m, 1368 m, 1230 m, 1208 m, 855 w cm$^{-1}$; yield, 33% based on starting isobutylene; 16% based on CuBr.

## B. Reaction of Dihalocarbenes with Primary Amines

The reaction of dihalocarbenes with primary amines affords isonitriles in good-to-poor-to-fair yields [28–50]. The dihalocarbenes are generated in situ from the reaction of bases on haloforms or by the thermal reaction of sodium trihaloacetates [35]. The reaction is thought to involve the steps shown in Eq. 14 [47]. This reaction is also known as the "Hofmann carbylamine reaction" [31–33a].

$$RNH_2 + {:}CX_2 \longrightarrow [R{-}\overset{+}{N}H_2{-}\overset{-}{C}X_2] \xrightarrow{\beta\text{-elim. HX}} [R{-}N{=}CHX] \xrightarrow{\alpha\text{-elim. HX}} R{-}NC \quad (14)$$

$$X = Cl \text{ or } Br$$

The use of X = F or I has not been reported.

Some typical examples of this reaction as described in the literature are shown in Table II. Further optimization studies of this reaction are required to improve the yields of isonitriles.

The use of additional sources of dihalocarbenes such as haloacetones or silver trihaloacetates should also be investigated.

An improved procedure for the Hofmann carbylamine synthesis of isonitriles involves the use of a phase-transfer catalyst ($C_6H_5$—$CH_2N^+$-$(C_2H_5)_3Cl^-$). The yields of the reaction varied from 44 to 60% when 50% aqueous sodium hydroxide was used [33b,c].

Although the carbylamine reaction to prepare isonitrile is one of the early methods, it was not widely used because of the low yields obtained. The advent of the phase-transfer catalyst has led to renewed interest in its preparative use to give isonitriles. For example, *t*-butylamine gives *t*-butyl isonitrile by this method in 60–73% yield (based on chloroform [33c]. (See Preparation 2-6.)

**CAUTION:** This method should be carried out in a well-ventilated hood because carbon monoxide and the obnoxious odor of isonitriles are produced. Certain isonitriles are very toxic, as in the case of 1,4-diisocyanobutane [13].

The reaction of amines with iron(II) tetraphenylphorphyrin dichlorocarbene complex also yielded isonitriles on pyrolysis [33d].

### *2-3. Preparation of Phenyl Isonitrile* [51]

$$C_6H_5NH_2 + CHBr_3 + 3NaH \xrightarrow{THF} C_6H_5\text{—}NC + 3NaBr + 3H_2 \qquad (14a)$$

To a flask containing 7.9 gm (0.33 mole) of sodium hydride in 100 ml of tetrahydrofuran is slowly added a mixture of 9.3 gm (0.1 mole) of aniline and 25.3 gm (0.10 mole) of bromoform. After the addition, the reaction is stirred for 1–2 hr at room temperature, and water is added (100 ml) dropwise. Ether (200 ml) is added and the ether layer washed four times with 50-ml portions of water, three times with 20-ml portions of dilute hydrochloric acid, and then with water. The resulting ether layer is dried over sodium sulfate, concentrated, and the residue distilled to afford 4.7 gm (45%), b.p. 52–53°C (13 mm Hg).

### *2-4. Preparation of* p*-Isonitrilobenzoic Acid* [40]

$$\begin{tikzcd}[column sep=small] p\text{-}H_2N\text{—}C_6H_4COOH + CHCl_3 \arrow[r, "CH_3OH", "NaOH"'] & p\text{-}CN\text{—}C_6H_4COONa \arrow[d, no head] & & \\ & {} \arrow[r, "HCl"] & p\text{-}CN\text{—}C_6H_4COOH + NaCl & (15) \end{tikzcd}$$

To a flask containing a solution of 27.4 gm (0.20 mole) of *p*-aminobenzoic acid and 13 ml (0.104 mole) of chloroform in 100 ml of methanol is first added 3.0 gm (0.075 mole) of sodium hydroxide and then 5 ml of a 60 : 40 mixture of methanol–chloroform (0.025 mole). Cooling is necessary after each addition in order to control the exothermic reaction. This operation is repeated for a total of 20 times, which takes about 2 hr. After the addition, the reaction mixture is heated to reflux for 5 min, the organic solvents removed under reduced pressure, and the solid residue is dissolved in 1100 ml of water. The water phase is extracted with 500 ml of cold ether containing 3% hydrochloric acid until the aqueous phase is acid to Congo Red. The ether is dried, concentrated, and the residue recrystallized from benzene–pentane to afford 10.0 gm (34%), m.p. > 300°C; IR, 4.70 μ (—NC).

### 2-5. *Preparation of* p-*Tolyl Isonitrile* [48]

$$p\text{-}CH_3C_6H_4\text{—}NH_2 + 3CCl_3COONa \longrightarrow p\text{-}CH_3C_6H_4\text{—}NC + 2CHCl_3 + 3CO_2 + 3NaCl \qquad (16)$$

To a flask containing 5.4 gm (0.05 mole) of *p*-toluidine in 100 ml of dry 1,2-dimethoxyethane is added 28 gm (0.15 mole) of sodium trichloroacetate. The reaction is slightly exothermic. The reaction mixture is refluxed for ½ hr, whereupon carbon dioxide is copiously evolved. The reaction mixture is filtered, the solid (10 gm) is washed with ether, and the combined reddish black filtrate concentrated. The residue is extracted with ether, washed with water, dried, and concentrated to afford a red-black oil, which, upon distillation, gives 2.5 gm (43%), b.p. 38°C (1 mm Hg), m.p. 19–20°C of a yellow liquid, IR, 4.69 μ (—NC).

### 2-6. *Preparation of Phenyl Isonitrile Using a Phase-Transfer Catalyst* [33b]

$$C_6H_5NH_2 + CHCl_3 + 3NaOH \xrightarrow[CH_2Cl_2]{C_6H_5CH_2N^+(CH_3)_3\,Cl^-} C_6H_5N{\equiv}C + 3\,NaCl^- \qquad (17)$$

**CAUTION:** The preparation should be carried out in a well-ventilated hood due to the pungent odor and toxicity of some isonitriles.

To a 500 ml round bottom flask equipped with a mechanical stirrer, a reflux condenser, a thermometer, and a dropping funnel is added 18.6 g (0.2 mole) aniline, 24.0 g (0.2 mole) of alcohol free chloroform, 0.5 g of benzyltrimethylammonium chloride and 60 ml of methylene chloride. Then 60 ml of 50% aqueous caustic solution (NaOH) is passed in one portion. After about a 10-min induction period, the methylene chloride starts to reflux, and the mixture is kept at 40°C (reflux temperature) by its own heat of reaction. After about 1 hr the refluxing ceases and the mixture is stirred for an additional 1 hr. The reaction mixture is diluted with water and the phenyl isonitrile extracted with methylene chloride. The latter

TABLE III

SYNTHESIS OF OTHER ISONITRILES BY PROCEDURE 2-6

| Isonitrile | % yield | b.p.°C | mm Hg | Ref. |
|---|---|---|---|---|
| *n*-Butyl | 60 | 40–42 | 11 | *a* |
| *t*-Butyl | 66–73 | 92–93 | 725 | *b* |
| $C_6H_5CH_2$ | 55 | 92–93 | 11 | *a* |
| *n*-$C_{12}H_{25}-$ | 41 | 115–118 | 0.1 | *a* |
| Cyclohexyl | 48 | 67–72 | 13 | *a* |
| $CH_3-$[c] | 24 | 59–60 | 760 | *b* |
| $C_2H_5-$[c] | 47 | 78–79 | 760 | *b* |

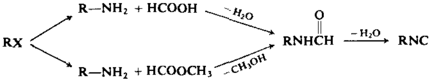
[a] W. P. Weber and G. W. Gokel, *Tetrahedron Letters* (17) 1637 (1972). [b] G. W. Gokel, R. P. Widera, and W. P. Weber, *Organic Synthesis* **55**, 96 (1976). [c] $CHBr_3$ used in place of $CHCl_3$.

extract is washed with water, then brine (5% NaCl), and is then dried over $MgSO_4$ or $K_2CO_3$. The product is isolated by distillation, to give 12 g (57%), b.p. 50–52°C (11 mm Hg).

Other isonitriles made by this process are shown in Table III.

## 3. ELIMINATION REACTIONS

*Isonitriles are obtained in high yields by the dehydration of N-monosubstituted formamides.* The formamides are easily prepared in high yields by reaction of a primary amine with methyl formate or formic acid. This method is useful *only if a functional group can be easily converted to a* primary amine or if primary amines are readily available as the starting material. These reactions are briefly described in Eq. 18.

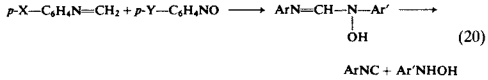


$$RX \to \left\{\begin{matrix} R{-}NH_2 + HCOOH \xrightarrow{-H_2O} \\ R{-}NH_2 + HCOOCH_3 \xrightarrow{-CH_3OH} \end{matrix}\right\} RNH\overset{O}{\overset{\|}{C}}H \xrightarrow{-H_2O} RNC \quad (18)$$

*Other eliminations used less frequently to afford nitriles are the dealcoholation of ethyl formimino ethers* (Eq. 19) and the decomposition of the adducts of *N*-methylene arylamines and nitrosoarenes, as shown in Eq. 20.

Gautier [3b, 52] first suggested that isonitriles be prepared by the dehydration of formamides of primary amines. Although he was not successful in his attempts, Hagedorn [53a,b] and later Corey [54] reported that

$$C_6H_5{-}N{=}CH{-}OC_2H_5 \xrightarrow{\text{base}} C_6H_5NC + C_2H_5OH \qquad (19)$$



$$p\text{-}X{-}C_6H_4N{=}CH_2 + p\text{-}Y{-}C_6H_4NO \longrightarrow ArN{=}CH{-}\underset{\displaystyle OH}{\underset{|}{N}}{-}Ar' \longrightarrow ArNC + Ar'NHOH \qquad (20)$$

X = H, Br, Cl, $CH_3$
Y = H, Cl
Ar = $p$-X-$C_6H_4$ and Ar′ = $p$-Y-$C_6H_4$

isonitriles could be obtained by this method using *p*-toluenesulfonyl chloride–pyridine.

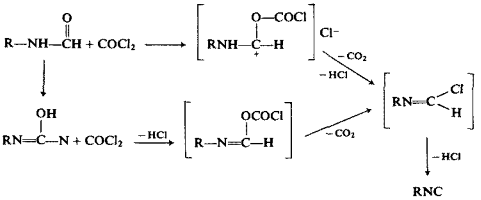
The most suitable dehydrating agents used for the dehydration of *N*-monosubstituted formamide are phosgene–triethylamine [55], phosgene–sodium hydroxide [55], benzenesulfonyl chloride–pyridine or quinoline [54, 56], *p*-toluenesulfonyl chloride–pyridine or quinoline [54, 56], and phosphorus oxychloride–pyridine [57a–c] or potassium *t*-butoxide [51]. Other dehydrating agents for the *N*-monosubstituted formamides are cyanuric chloride [58], thionyl chloride [59], phosphorus tribromide [59], phosphorus trichloride [59], phosphorus pentachloride [59], phosphorus pentoxide [59], and triphenylphosphine dibromide [60], all in the presence of bases (tertiary amines, sodium hydroxide, alkali carbonates or alkoxides).

Recently, the preparation of polymers with isonitriles was reported. These were made by the dehydration of the corresponding formamides with $POCl_3/Et_3N$. These polymers are further polymerized with catalytic amounts of $NiCl_2$ [62c].

## A. Phosgene Method

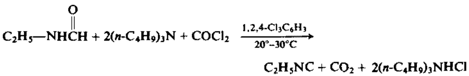
Ugi and co-workers [55, 61] have reported that phosgene in the presence of trimethyl- or triethylamine dehydrates *N*-monosubstituted formamides to isonitriles in good yields. Other tertiary amines that are effective are the following: tri-*n*-butylamine, *N,N*-dimethylcyclohexylamine, *N,N*-diethylaniline, pyridine, or quinoline. Two methods have been found effective: (1) addition of phosgene to a solution of the *N*-monosubstituted formamide and tertiary amine in methylene chloride at 20–30°C; (2) addon of phosgene as in (1) without cooling until the refluxing ceases. In both cases, ammonia is added at the end, ammonium chloride filtered and concentrated to give the crude product. Several examples of isonitriles prepared by Methods 1 or 2 are shown in Table IV. A patent has appeared wherein an aqueous solution or a suspension of an inorganic base or basic salt is used in place of the tertiary amines in the phosgene method [62a]. An example of this modification is given in Table IV. The addition of amines to the aqueous base was reported to be a superior method [62d].

The reaction of phosgene with *N*-alkyl formamides may proceed via a chloroformyl ester type intermediate as shown in Eq. 21. The exact mechanism of this reaction still remains to be determined.



(21)

### *3-1. Preparation of Ethyl Isonitrile* [61]



$$C_2H_5\text{—NH}\overset{O}{\overset{\|}{C}}H + 2(n\text{-}C_4H_9)_3N + COCl_2 \xrightarrow[20°\text{–}30°C]{1,2,4\text{-}Cl_3C_6H_3} C_2H_5NC + CO_2 + 2(n\text{-}C_4H_9)_3NHCl \qquad (22)$$

**CAUTION:** Use a well-ventilated hood, and take all precautions necessary before working with phosgene.

To a 10-1, three-necked flask equipped with a stirrer, a wide gas inlet tube dipping to the bottom of the flask, and a wide gas outlet tube is added 730 gm (10.0 moles) of *N*-ethylformamide, 5.0 liters of tri-*n*-butylamine, and 3.0 l of 1,2,4-trichlorobenzene. The flask is cooled and stirred while 1.0 kg (10.1 moles) of phosgene is added at 20–30°C at such a rate as to complete the addition in 3–4 hr. After the addition, the reaction mixture is stirred for 1 hr and 100 gm of ammonia is slowly added. The crude product (430 gm) is distilled off at 30–50°C at 150 mm Hg and collected in dry-ice traps. Fractional distillation using a helix-packed column affords 358 gm (65%), b.p. 32–35°C (120 mm Hg).

## TABLE IV

Preparation of Substituted Isonitriles by the Phosgene Dehydration of *N*-Alkyl or *N*-Aryl Formamides

| N-Substituted formamide $RNH\overset{O}{\overset{\|}{C}}H$ (moles), R= | $R'_3N$ (ml) R'= | Solvent (ml) | $COCl_2$ (moles) | Reaction conditions | | Yield RNC (%) | B.p., °C (mm Hg) or m.p., °C | Method (1) or (2) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Temp. (°C) | Time (hr) | | | | |
| $C_2H_5$<br>(10.0) | *n*-Bu<br>(5000) | 1,2,4-$Cl_3C_6H_3$<br>(3000) | 10.1 | 20–30 | 3–4 | 65 | 32–35(120) | 1 | *a* |
| $C_2H_5O\overset{O}{\overset{\|}{C}}—CH_2$<br>(1.0) | $C_2H_5$<br>(320) | $CH_2Cl_2$<br>(900) | 1.06 | 40–41 | 3–4 | 77 | 76–78(4) | 2 | *a* |
| $(CH_3)_3CO\overset{O}{\overset{\|}{C}}—CH_2$<br>(0.30) | $C_2H_5$<br>(100) | $CHCl_3$<br>(150) | 0.30 | 25 | 1 | 77 | 87–89(15) | 1 | *b* |
| $(CH_3)_3C$<br>(10.0) | $CH_3$<br>(1300) | 1,2-$Cl_2C_6H_4$<br>(7000) | 10.1 | 179 | 3–4 | 82 | 90–92(750) | 2 | *a* |
| (10.0) | *n*-Bu<br>(5400) | 1,2,4-$Cl_3C_6H_3$<br>(2500) | 10.1 | 10–20 | 3–4 | 78 | 90–92(750) | 1 | *a* |
| (1.5) | NaOH<br>(6.7) | $H_2O$(650)<br>1,2-$Cl_2C_6H_4$<br>(1000) | 1.4 | 0–5 | 1 | 71 | 92(760) | — | *c* |
| $C_6H_{11}$(cyclo)<br>(10) | $C_2H_5$<br>(3200) | $CH_2Cl_2$<br>(4500) | 10.1 | 40–41 | 3–4 | 88 | 67–72(14) | 2 | *a* |
| 2,7-Dinaphthyl<br>(0.5) | $C_2H_5$<br>(320) | $CH_2Cl_2$<br>(1200) | 1.01 | 40–41 | 1 | 93 | 142–144 | 2 | *a* |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 3-Methoxy-4′-*t*-butyl diphenyl ether-4- (0.64) | $C_2H_5$ (165) | $CH_2Cl_2$ (1000) | 0.76 | 0–10 | 1 | — | 85–86 | 1 | *d* |
| Pyridine-3- (0.1) | $C_2H_5$ (32) | $CH_2Cl_2$ (150) | 0.1 | 0 | 1 | 70 | — | 1 | *e* |
| $C_6H_5CH_2$ (0.5) | $CH_3$ (66) | $CH_2Cl_2$ (500) | 0.5 | −35 to −15 | 1 | 83 | 45–47 (0.001) | 1 | *f* |
| $(C_2H_5)_2N$ (0.1) | $CH_3$ (33) | $CH_2Cl_2$ (150) | 0.1 | 0 | 1 | — | 39(16) | 1 | *g* |
| $(n\text{-}C_4H_9)_2N$ (0.1) | $CH_3$ (33) | $CH_2Cl_2$ (150) | 0.1 | 0 | 1 | — | 42(0.1) | 1 | *g* |
| 2,6-xylyl (0.1) | NaOH 45% + zinc pH 11 | Sat. NaCl (30)<br>Ethylene chloride (80) | 0.16 | 0–5 | — | 0 | — | — | *h* |
| (12.5) | 45% NaOH to give pH 11 | Sat. NaCl (3000)<br>Ethylene chloride (7100)<br>Diethylene aniline (100 g) | 20 | 30 | 1 | 5 | m.p. 68–70°C | — | *h* |

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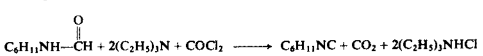
[a] I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer, and K. Offermann, *Angew. Chem. Int. Ed.* **4,** 472 (1965). [b] I. Ugi, W. Betz, U. Fetzer, and K. Offermann, *Chem. Ber.* **94,** 2814 (1961). [c] Farbenfabriken Bayer A. G. Fr. Demande 2,002,568 (1969); *Chem. Abstr.* **72,** 89826f (1970). [d] I. Hammann, P. Hoffmann, G. Unterstenhoefer, H. Kleimann, D. Marquarding, K. Offermann, and I. Ugi, S. African Pat. 69-01,922 (1969). [e] R. Neidlein, *Arch. Pharam.* **299** (7), 603 (1966). [f] I. Ugi and S. Betz, German Pat. 1,177,146 (1964). [g] H. Bredereck, B. Föhlisch, and K. Walz, *Angew. Chem.* **74,** 388 (1962). [h] P. Hoffmann, D. Marquarding, V. Ugi, D. Arlt, and H. Hagemann, U.S. Pat. 3,794,674 (1974).

### *3-2. Preparation of Cyclohexyl Isonitrile* [61]

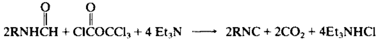


$$C_6H_{11}NH{-}\overset{O}{\overset{\|}{C}}H + 2(C_2H_5)_3N + COCl_2 \longrightarrow C_6H_{11}NC + CO_2 + 2(C_2H_5)_3NHCl \tag{23}$$

**CAUTION:** Use a well-ventilated hood and take all precautions before using phosgene.

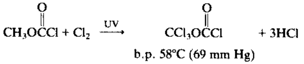
To a flask equipped as in Preparation 3-1 is added 1.27 kg (10.0 moles) of *N*-cyclohexylformamide, 3.20 liters of triethylamine, and 4.50 liters of methylene chloride. The solution is stirred while phosgene is rapidly added (300–400 gm/hr) to cause vigorous refluxing. Refluxing ceases after 1.04 kg (10.2 moles) of phosgene have been added and the addition is stopped. The reaction mixture is cooled to 22–25°C, 400 gm (23.5 moles) of ammonia gas added over a period of 1–2 hr, the mixture filtered then concentrated under reduced pressure, and the residue distilled to afford 955 gm (88%), b.p. 67–72°C (14 mm Hg).

A modification of the phosgene method involves the use of diphosgene as reported by Skorna and Igo [62b] and later by Efraty, Feinstein, Wackerle, and Goldman [62c].



$$2RNH\overset{O}{\overset{\|}{C}}H + ClC\overset{O}{\overset{\|}{O}}CCl_3 + 4\,Et_3N \longrightarrow 2RNC + 2CO_2 + 4Et_3NHCl \tag{24}$$

The preparation of diphosgene was reported to be by the UV (ultraviolet) chlorination of methyl chloroformate [62c]. Its advantage is that it can be more easily shipped and handled than phosgene. The use of diphosgene to prepare isonitriles is described in Table V.



$$CH_3O\overset{O}{\overset{\|}{C}}Cl + Cl_2 \xrightarrow{UV} \underset{\text{b.p. 58°C (69 mm Hg)}}{CCl_3O\overset{O}{\overset{\|}{C}}Cl} + 3HCl \tag{25}$$

## B. Arylsulfonyl Chloride Method*

Hertler and Corey [54] reported that *p*-toluenesulfonyl chloride reacts with *N*-alkylformamides in pyridine to afford isonitriles as shown in Eq. 26.

This reaction appears to be quite general and is effective for the prepara-

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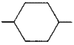
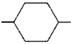
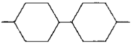
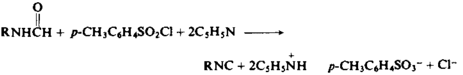
* From Hertler and Corey [54].

TABLE V

PREPARATION OF ISONITRILES BY MEANS OF THE DIPHOSGENE REAGENT

| Isonitrile | % Yield with $\mathrm{CCl_3O\overset{\overset{O}{\|}}{C}Cl}$ | % Yield with $COCl_2$ | Ref. |
|---|---|---|---|
| $CH_3$ | 47 | 37 | [62b] |
| $t\text{-}(CH_3)_3C\text{-}$ | 97 | 82 | [62b] |
|  | 98 | 88 | [62b] |
| $C_6H_5CH_2$ | 95 | 82 | [62b] |
|  | 76 | ? | [62c] |
|  | 72 | 72 | [62c] |

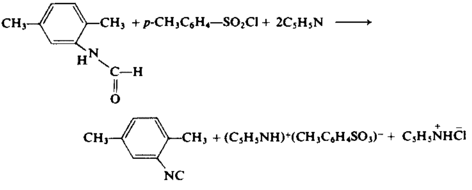


$$\mathrm{RNH\overset{\overset{O}{\|}}{C}H} + p\text{-}CH_3C_6H_4SO_2Cl + 2C_5H_5N \longrightarrow RNC + 2C_5H_5\overset{+}{N}H \quad p\text{-}CH_3C_6H_4SO_3^- + Cl^- \tag{26}$$

tion of aliphatic, alicyclic, and aromatic substituted isonitriles. In some cases, benzenesulfonyl chloride is inferior to *p*-toluenesulfonyl chloride.

Pure aliphatic isonitriles may be obtained by removing them as they are formed from the reaction medium by the use of reduced pressure [63]. Several examples of this reaction are shown in Table VI.

### *3-3. Preparation of 2,5-Dimethylbenzoisonitrile* [64]

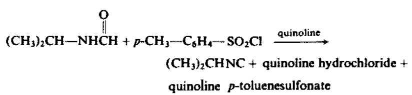

CH₃
CH₃
+ p-CH₃C₆H₄—SO₂Cl + 2C₅H₅N
H
N
C—H
O
CH₃
CH₃
+ (C₅H₅NH)⁺(CH₃C₆H₄SO₃)⁻ + C₅H₅N̊HCl
NC

(27)

To a flask containing 40 ml (0.50 mole) of pyridine is added all at once, with stirring, 7.46 gm (0.05 mole) of *N*-formyl-*p*-xylidene and 13.3 gm (0.07 mole) of *p*-toluenesulfonyl chloride to form a solution that turns orange-red. After stirring for 1 hr at room temperature, the solution turns green, and after an additional $\frac{1}{2}$ hr, the solution is cooled. Chipped ice is added, then the mixture poured into ice water and extracted with ether; the ether extract is washed three times with cold water, dried, concentrated; and the residue is distilled under reduced pressure to afford 3.3 gm (50%), b.p. 87.5–90°C (12 mm Hg).

NOTE: Distill behind a protective shield in the hood.

### *3-4. Preparation of Isopropyl Isonitrile* [64a]



$$(CH_3)_2CH{-}NH\overset{\overset{\displaystyle O}{\|}}{C}H + p\text{-}CH_3{-}C_6H_4{-}SO_2Cl \xrightarrow{\text{quinoline}} (CH_3)_2CHNC + \text{quinoline hydrochloride} + \text{quinoline } p\text{-toluenesulfonate} \tag{28}$$

To a flask containing 100 ml (0.85 mole) of distilled quinoline is added with stirring 41 gm (0.214 mole) of *p*-toluenesulfonyl chloride (see Note), and the solution is warmed to 75°C. Then 18.4 gm (0.212 mole) of isopropylformamide is added and the pressure of the system is reduced to 70 mm Hg. The isopropylisonitrile as it forms distills into a liquid nitrogen-cooled receiver. (Dry ice is not as effective but may be used.) The product is redistilled to afford 4.2 gm (30%), b.p. 88–89°C (735 mm Hg).

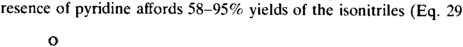
NOTE: Use of benzenesulfonyl chloride in place of the *p*-toluenesulfonyl chloride gave lower yields of the isonitrile.

For a comparison of the use of benzenesulfonyl chloride versus phosgene for the preparation of *t*-butyl isonitrile, see [62d].

## C. Phosphorus Oxychloride Method

The phosphorus oxychloride method has the advantage of being safer than the phosgene method.

The reaction of phosphorus oxychloride with aliphatic formamides in the presence of pyridine affords 58–95% yields of the isonitriles (Eq. 29).



$$R{-}NH\overset{\overset{\displaystyle O}{\|}}{C}H + POCl_3 + 4C_5H_5N \longrightarrow 2RNC + 3C_5H_5NHCl + C_5H_5NHPO_3 \tag{29}$$

TABLE VI

PREPARATION OF ISONITRILES BY THE REACTION OF MONOSUBSTITUTED FORMAMIDES WITH *p*-TOLUENESULFONYL CHLORIDE

| $R{-}NH\overset{\overset{O}{\|}}{C}H$ (moles), R = | $p$-$CH_3C_6H_4SO_2Cl$ (moles) | Base[e] (ml) | Reaction conditions<br>Temp. (°C) | <br>Time (hr) | <br>Pressure (mm Hg) | Yield RNC % | B.p., °C (mm) or m.p., °C | Ref. |
|---|---|---|---|---|---|---|---|---|
| 2,5-Dimethylphenyl<br>(0.05) | 0.07 | Pyridine<br>(40) | 25 | 1½ | 760 | 50 | 87.5–90<br>(12) | *a* |
| 3β-Acetoxy-20α-formamidopregnane-5<br>(0.00039) | 0.0005 | (2.5) | 25 | 1½ | 760 | 84 | 141–151 | *a* |
| Methyl<br>(0.25) | 0.38 | Quinoline<br>(1.0) | 75 | | 60 | 50–74 | 59–60<br>(760) | *b*, *c* |
| Cyclobutyl<br>(0.08) | 0.13 | (0.33) | 50 | 1 | 5–10 | 24 | — | *b* |
| Isopropyl<br>(0.21) | 0.21 | (100) | 75 | 1 | 70 | 30 | 88–89<br>(735) | *d* |
| Ethanol<br>(1.0) | 2.0 | Pyridine<br>(550) | 10 | 6 | 760 | 31[g] | 57–57.5<br>(760) | *f* |
| $(CH_3)_3C$<br>(1.0) | 0.95 | NaOH<br>(0.9)<br>Solvent:<br>1,2-$Cl_2C_6H_4$<br>(500) | 25 | 1 | 760 | 49 | 92 (760) | *h* |

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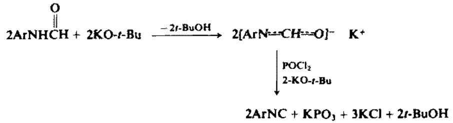
[a] W. R. Hertler and E. J. Corey, *J. Org. Chem.* **23**, 1221 (1958). [b] J. Casanova, Jr., R. E. Schuster, and N. D. Werner, *J. Chem. Soc.* 4280 (1963). [c] R. E. Schuster, J. E. Scott, and J. Casanova, Jr., *Org. Syn.* 46, 75 (1966). [d] H. W. Johnson, Jr., and P. H. Daughhetee, Jr., *J. Org. Chem.* **29**, 246 (1964). [e] Practical grades must be distilled prior to use. Undistilled bases afford isocyanates as a major contaminant. [f] D. S. Matteson and R. A. Bailey, *J. Amer. Chem. Soc.* **90**, 3761 (1968). [g] 2-Isocyanoethyl *p*-toluenesulfonate. [h] Farbenfabriken Bayer A. G. Fr. Demande 2,002,568 (1969).

Aromatic isonitriles are only obtained in 7–54% yields using pyridine as the base, but are obtained in 88% by the use of potassium *t*-butoxide, as shown in [Eq. 30].

Several examples of this method for the aliphatic and aromatic series are shown in Table VII.



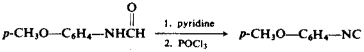
$$2\mathrm{ArNH\overset{\overset{\displaystyle O}{\|}}{C}H} + 2\mathrm{KO}\text{-}t\text{-}\mathrm{Bu} \xrightarrow{-2t\text{-}\mathrm{BuOH}} 2[\mathrm{ArN\cdots CH\cdots O}]^- \ \mathrm{K}^+ \xrightarrow[2\text{-}\mathrm{KO}\text{-}t\text{-}\mathrm{Bu}]{\mathrm{POCl_2}} 2\mathrm{ArNC} + \mathrm{KPO_3} + 3\mathrm{KCl} + 2t\text{-}\mathrm{BuOH} \qquad (30)$$

Recently, it has been reported that the use of diisopropylamine in place of pyridine gives isonitriles (also aromatic types) in yields of about 89% [64b]. For more details, see Table VIII (p. 230).

As seen, the method in Table VIII gives yields of isonitriles comparable to the phosgene or the diphosgene (trichloromethyl carbone chloridate) methods.

The use of the less sterically hindered diethylamine in place of diisopropylamine gives no trace of isonitrile [64b].

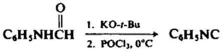
### 3-5. *Preparation of* p-*Methoxyphenyl Isonitrile* [65]



$$p\text{-}\mathrm{CH_3O{-}C_6H_4{-}NH\overset{\overset{\displaystyle O}{\|}}{C}H} \xrightarrow[2.\ \mathrm{POCl_3}]{1.\ \text{pyridine}} p\text{-}\mathrm{CH_3O{-}C_6H_4{-}NC} \qquad (31)$$

To an ice-cooled flask containing a solution of 10.5 gm (0.065 mole) of *p*-methoxyformanilide in 37.1 gm (0.47 mole) of pyridine and 13.0 ml (0.16 mole) of chloroform is added dropwise at 0°C 6.12 gm (0.040 mole) of phosphorus oxychloride. The solution is stirred for $1\frac{1}{2}$ hr at room temperature and then added to 55 ml of ice-water. The water layer is extracted with two 10-ml portions of chloroform; the combined chloroform layer is dried and distilled under reduced pressure, to afford 3.5 gm (40%), b.p. 76γC (1.0 mm Hg), IR 2137 cm$^{-1}$ (R—NC).

### 3-6. *Preparation of Phenyl Isonitrile* [59, 65]



$$\mathrm{C_6H_5NH\overset{\overset{\displaystyle O}{\|}}{C}H} \xrightarrow[2.\ \mathrm{POCl_3},\ 0^\circ\mathrm{C}]{1.\ \mathrm{KO}\text{-}t\text{-}\mathrm{Bu}} \mathrm{C_6H_5NC} \qquad (32)$$

To a flask containing a solution of 13.5 gm (0.11 mole) of formanilide in

(*text continues on p. 230*)

## TABLE VII

### Preparation of Isonitriles by the Dehydration of Monosubstituted Formamides with Phosphorus Oxychloride

| $\mathrm{RNH\overset{O}{\overset{\|}{C}}H}$ (moles) | $POCl_3$ (moles) | Base (moles) | Solvent (ml) | Reaction conditions | | Yield RNC (%) | B.p., °C (mm Hg) or m.p., °C | $n_D$ (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Temp. (°C) | Time (hr) | | | | |
| | | Pyridine | Pet. ether (40°–60°C) | | | | | | |
| Cyclohexyl (0.5) | 0.3 | 3.1 | 150 | 0 | 1/4 | 83 | 56–68 (11) | 1.4488–1.4501 (25) | *a* |
| | | | | 60 | 1/6 | | | | |
| *t*-Butyl (0.5) | 0.3 | 3.1 | 150 | 0 | 1/4 | 95 | 91–92 (730) | — | *a* |
| | | | | 60 | 1/6 | | | | |
| *n*-Butyl (0.5) | 0.3 | 3.1 | 150 | 0 | 1/4 | 61 | 116–117 (730) | — | *a* |
| | | | | 60 | 1/6 | | | | |
| Isopropyl (0.5) | 0.3 | 3.1 | 150 | 0 | 1/4 | 58 | 87–88 (730) | — | *a* |
| | | | | 60 | 1/6 | | | | |
| Benzyl (0.5) | 0.3 | 3.1 | 150 | 0 | 1/4 | 56 | 92–94 (11) | — | *a* |
| | | | | 60 | 1/6 | | | | |
| Phenyl (0.5) | 0.3 | 3.1 | 150 | 0 | 1/4 | 7[h] | 50–51 (11) | — | *a* |
| | | | | 60 | 1/6 | | | | |
| *o*-Tolyl (0.5) | 0.3 | 3.1 | 150 | 0 | 1/4 | 54[i] | 62–64 (11) | — | *a* |
| | | | | 60 | 1/6 | | | | |
| *p*-Tolyl (0.5) | 0.3 | 3.1 | 150 | 0 | 1/4 | 35 | 71–72 (11) | — | *a* |
| | | | | 60 | 1/6 | | | | |
| *p*-Methoxyphenyl (0.5) | 0.3 | 3.1 | 150 | 0 | 1/4 | 31 | 76–87 (1) | — | *a* |
| | | | | 60 | 1/6 | | | | |
| | | | $CHCl_3$ | | | | | | |
| *p*-Methoxyphenyl (0.065) | 0.040 | 0.47 | 13 | 25 | 1½ | 40 | 76 (1) | — | *c* |

*(continues)*

TABLE VII (*Continued*)

| $RNHCHO$ (moles) | $POCl_3$ (moles) | Base (moles) | Solvent (ml) | Reaction conditions Temp. (°C) | Reaction conditions Time (hr) | Yield RNC (%) | B.p., °C (mm Hg) or m.p., °C | $n_D$ (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| *cis*-2,2,4,4-Tetramethyl cyclobutyl-1,3- (0.1) | 0.156 | 1.25 | Pet. ether 30°–60°C<br>65 | 0<br>55 | 1/6<br>1/2 | 41 | 57.5–58 | — | *d* |
| *trans*-2,2,4,4-Tetramethylcyclobutyl-1,3- (0.1) | 0.156 | 1.25 | 65 | 0<br>55 | 1/16<br>1 | 69 | 138–139 | — | *d* |
| 2-Formylamino-1-phenyl-1-ethanol (0.06) | 0.13 | 1.9 | — | 0<br>65 | 1/12<br>1/2 | 49[f] | 70–72 (0.02) | — | *e* |
| Isopropyl (0.5) | 0.3 | 1.9 | $CHCl_3$<br>200 | 0<br>20 | 1/4<br>1/2 | 54 | 87–88 (730) | — | *a* |
| *n*-Butyl (0.5) | 0.3 | 1.9 | 200 | 0<br>20 | 1/4<br>1/2 | 62 | 116–117 (730) | — | *a* |
| *t*-Butyl (0.5) | 0.3 | 1.9 | 200 | 0<br>20 | 1/4<br>1/2 | 93 | 91–92 (730) | — | *a* |
| Cyclohexyl (0.5) | 0.3 | 1.9 | 200 | 0<br>20 | 1/4<br>1/2 | 85 | 56–58 (11) | — | *a* |
| Benzyl (0.05) | 0.3 | 1.9 | 200 | 0<br>20 | 1/4<br>1/2 | 64 | 92–94 (11) | — | *a* |
| *o*-Tolyl (0.5) | 0.3 | 1.9 | 200 | 0<br>20 | 1/4<br>1/2 | 37[i] | 62–64 (11) | — | *a* |
| 2,6-Dimethylphenyl (0.5) | 0.3 | 1.9 | 200 | 0<br>20 | 1/4<br>1/2 | 42 | 55–58 (1) | — | *a* |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Cyclohexyl | 0.066 | KO-*t*-Bu<br>0.3 | *t*-BuOH<br>100 | 0 | 1/12 | 85 | 56–58 (11) | — | *a* |
| (0.1) | | | | 40–50 | 1/2 | | | | |
| Benzyl | 0.066 | 0.3 | 100 | 0 | 1/12 | 56 | 92–94 (11) | — | *a* |
| (0.1) | | | | 40–50 | 1/2 | | | | |
| Phenyl | 0.066 | 0.3 | 100 | 0 | 1/12 | 40–56[h] | 50–51 (11) | — | *a, c* |
| (0.1) | | | | 40–50 | 1/2 | | | | |
| *o*-Tolyl | 0.066 | 0.3 | 100 | 0 | 1/12 | 63–72[i] | 62–64 (11) | 1.5212–<br>1.5222<br>(25) | *a, g* |
| (0.1) | | | | 40–50 | 1/2 | | | | |
| *p*-Tolyl | 0.066 | 0.3 | 100 | 0 | 1/12 | 66 | 71–72 (1) | — | *a* |
| (0.1) | | | | 40–50 | 1/2 | | 20–21 | | |
| *o*-Chlorophenyl | 0.066 | 0.3 | 100 | 0 | 1/12 | 43 | 58–59 (1) | — | *a* |
| (0.1) | | | | 40–50 | 1/2 | | 26–28 | | |
| *p*-Chlorophenyl | 0.066 | 0.3 | 100 | 0 | 1/12 | 43–54 | 61–64 (1) | — | *a, c* |
| (0.1) | | | | 40–50 | 1/2 | | 72–73 | | |
| *m*-Nitrophenyl | 0.066 | 0.3 | 100 | 0 | 1/12 | 25 | 97–99 | — | *a* |
| (0.1) | | | | 40–50 | 1/2 | | | | |
| *p*-Nitrophenyl | 0.066 | 0.3 | 100 | 0 | 1/12 | 41 | 119–120 | — | *a* |
| (0.1) | | | | 40–50 | 1/2 | | | | |
| 2,6-Dimethylphenyl | 0.066 | 0.3 | 100 | 0 | 1/12 | 88 | 55–58 (1) | — | *a* |
| (0.1) | | | | 40–50 | 1/2 | | 72–73 | | |
| β-Naphthyl | 0.066 | 0.3 | 100 | 0 | 1/12 | 60 | 100–102 (1) | — | *a* |
| (0.1) | | | | 40–50 | 1/2 | | 59–60 | | |

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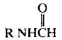
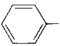
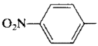
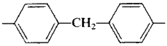
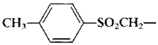
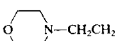
[a] I. Ugi and R. Meyr, *Chem. Ber.* **93**, 239 (1960). [b] I. Ugi, R. Meyr, M. Lipinski, F. Bodensheim, and F. Rosendahl, *Org. Syn.* **41**, 13 (1961). [c] J. Casanova, Jr., N. D. Werner, and R. E. Schuster, *J. Org. Chem.* **31**, 3473 (1966). [d] F. Lautenschläger and G. F. Wright, *Canad. J. Chem.* **41**, 863 (1963). [e] J. Hagedorn and H. Etling, German Pat. 1,168,895 (1964); J. Hagedorn, U. Eholzer, and H. Etling, *Chem. Ber.* **98**, 193 (1965). [f] Structure of the product is 2-chloro-2-phenylethylisonitrile. [g] I. Ugi and R. Meyr, *Org. Syn.* **41**, 101 (1961). [h] The blue, nonvolatile reaction product of phenylisonitrile is the tetramer. See C. Grundmann, *Chem. Ber.* **91**, 1380 (1958). [i] *o*-Tolylisonitrile is somewhat unstable and the reaction should be worked up without excessive heating periods. The product should be stored at Dry Ice temperatures.

TABLE VIII

PREPARATION OF ISONITRILES BY THE DEHYDRATION OF MONOSUBSTITUTED FORMAMIDE WITH PHOSPHORUS OXYCHLORIDE AND DIISOPROPYLAMINE [64b][a]

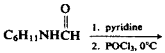
|  $RNHC(=O)H$ | % Yield RNC | M.p. °C | B.p. °C (mm Hg) |
|---|---|---|---|
|  | 53 | — | 36–38 (0.5) |
|  | 77 | 115–118 (from hexane) | |
|  | 89 | 131–133 (from hexane) | |
|  | 68 | 112–114 (from methylene chloride and hexane) | |
|  | 68 | — | 63–64 (0.2) |

[a] **General Procedure Used:**

To a solution or suspension of the preceding formamide (0.1 mole for mono- and 0.045 mole for bis-formamide) in 100 ml methylene, chloride and diisopropylamine (0.27 mole) was added dropwise at 0°C with stirring 0.11 mole of phosphoryl chloride. The reaction is stirred for 1 hr at 0°C if a solution was obtained and for 8 hr at about 25°C for sparingly soluble formamides. The addition of 20.0 g $Na_2CO_3$ in 100 ml water is added at such a rate as to maintain 25–30°C. After stirring for 1 hr at room temperature 100 ml of water and 50 ml methylene chloride is added. The organic layer is separated and washed with water (300 ml), dried using $Na_2SO_4$, and concentrated to give the residues, which are either distilled under reduced pressure or recrystallized from the solvent shown in the present table.

140 ml (0.3 mole) of potassium *t*-butoxide in *t*-butanol is added dropwise with stirring and cooling 10.2 gm (0.067 mole) of phosphorus oxychloride over a 5-min period. The solution is heated to 50°C for 5 min, cooled to room temperature, 10 gm of dry ice added slowly, the solution poured into 750 ml of ice water and extracted with four 30-ml portions of pentane. The combined pentane extract is washed with two 50-ml portions of ice water, dried, concentrated, and the residue distilled under reduced pressure to afford 4.44 gm (40%), b.p. 55°C (15 mm Hg). The product immediately forms the blue tetramer.

### 3-7. *Preparation of Cyclohexyl Isonitrile* [59, 66a]



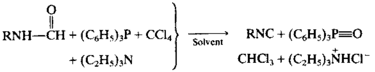
$$C_6H_{11}NH\overset{\overset{O}{\|}}{C}H \xrightarrow[\text{2. } POCl_3,\ 0°C]{\text{1. pyridine}} C_6H_{11}NC \qquad (33)$$

To a three-necked flask equipped with a condenser, ground glass stirrer, dropping funnel, and thermometer is added with stirring 127 gm (1.0 mole) of *N*-cyclohexylformamide, 500 ml (6.2 moles) of pyridine and 300 ml of petroleum ether (b.p. approx. 30–60°C). The solution is cooled to 0°C, and 92 gm (0.60 mole) of phosphorus oxychloride is added dropwise over a $\frac{1}{2}$-hr period. After the addition, the reaction mixture is refluxed for 10–20 min, cooled to 0–5°C, 800 ml of ice water slowly added, and the organic phase separated. The water layer is extracted with three 60-ml portions of petroleum ether, combined with the previously separated organic layer, washed with three 100-ml portions of water, dried, then concentrated, and the residue is distilled (see Note) to afford 73–79 gm (67–72%), b.p. 56–68°C (11 mm Hg), $n_D^{25}$ 1.4488–1.4501.

NOTE: Rapid distillation from a 50-cm spinning band column at a pot temperature not over 90°C affords little resinification of the product. At the end the isonitrile odor may be removed from the equipment by washing with 5% methanolic sulfuric acid solution.

## D. Triphenylphosphine Method

The joint action of triphenylphine [$(C_6H_5)_3P$]; $CCl_4$, and triethylamine on monosubstituted aliphatic and aromatic formamide is reported to give high yields of isonitriles [66b,c, 94].

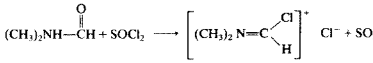


$$\left.\begin{array}{l} RNH{-}\overset{\overset{O}{\|}}{C}H + (C_6H_5)_3P + CCl_4 \\ \qquad + (C_2H_5)_3N \end{array}\right\} \xrightarrow[\text{Solvent}]{} \begin{array}{l} RNC + (C_6H_5)_3P{=}O \\ CHCl_3 + (C_2H_5)_3\overset{+}{N}HCl^- \end{array} \qquad (34)$$

Using a 20% excess of triphenylphosphine gives approximately 90% yields of isonitriles in the case of $n$-$C_4H_9NC$ and $C_6H_5NC$ and $C_6H_5CH_2NC$. For related work, see [66d].

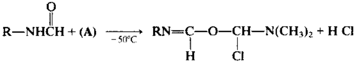
## E. Thionyl Chloride–DMF Method

Walborsky and Niznik [95] reported the Vilsmeier reagent (chlorodimethylformininium chloride) is a convenient dehydrating agent for formamides to give isonitriles. The reagent is prepared, in situ, from thionyl chloride and DMF (*N,N*-dimethylformamide) and must be used at approximately, −50°C in order to avoid side reactions with DMF.



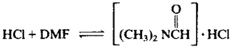
$$(CH_3)_2NH\text{—}\overset{O}{\overset{\|}{C}}H + SOCl_2 \longrightarrow \left[(CH_3)_2N{=}C\begin{smallmatrix}Cl\\ \\ H\end{smallmatrix}\right]^+ Cl^- + SO_2 \qquad (35)$$

**(A)**

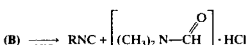


$$R\text{—}NH\overset{O}{\overset{\|}{C}}H + (A) \xrightarrow[-50°C]{} RN{=}\underset{H}{\underset{|}{C}}\text{—}O\text{—}\underset{Cl}{\underset{|}{C}}H\text{—}N(CH_3)_2 + HCl \qquad (36)$$

**(B)**



$$HCl + DMF \rightleftharpoons \left[(CH_3)_2N\overset{O}{\overset{\|}{C}}H\right]\cdot HCl \qquad (37)$$



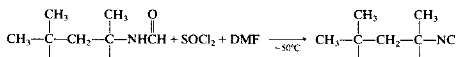
$$(B) \xrightarrow[25°C]{} RNC + \left[(CH_3)_2N\text{—}\overset{O}{\overset{/\!/}{C}}H\right]\cdot HCl \qquad (38)$$

**(C)**

$$2\,(C) + Na_2CO_3 \longrightarrow DMF + 2NaCl + CO_2 + H_2O \qquad (39)$$

Some of the typical isonitriles prepared by this method are shown in Table IX.

### *3-8. Preparation of 1,1,3,3-Tetramethylbutylisonitrile* [95]



$$CH_3\text{—}\underset{CH_3}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}\text{—}CH_2\text{—}\underset{CH_3}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}\text{—}NH\overset{O}{\overset{\|}{C}}H + SOCl_2 + DMF \xrightarrow[-50°C]{} CH_3\text{—}\underset{CH_3}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}\text{—}CH_2\text{—}\underset{CH_3}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}\text{—}NC \qquad (40)$$

To a stirred solution of 83.0 g (0.528 mole) of *N*-(1,1,3,3-tetramethylbutyl) formamide in 1 l of DMF was added dropwise, under a nitrogen atmosphere, a solution made up of thionyl chloride (40.3 ml, 0.55 mole) dissolved in 150 ml of DMF. The addition was at such a rate that the temperature did not exceed −50°C. After the addition, the cooling bath was removed momentarily to allow the temperature to increase to −35°C and then it was replaced while 118.0 g (1.11 mole) of sodium carbonate (anhydrous grade) was added. Then the cooling bath was removed and the reaction mixture was diluted with ice-cold water in a separatory funnel and then extracted with pentane. The pentane extract was dried over sodium sulfate and concentrated, and the product distilled to yield 68.4 g (93%

TABLE IX

Isonitriles by the $SOCl_2$-DMF Method[a]

| RNC | Reaction Scale | % Yield |
|---|---|---|
| | 0.10 | 87 |
| $n$-$C_6H_{12}$ | 0.13 | 82 |
| $t$-$(CH_3)_3C$— | 0.20 | 55 |
| $C_6H_5CH_2$ | 0.12 | 63 |
| $(C_6H_5)_3C$— | 0.27 | 95 |
| $C_6H_5$ | 0.18 | 60 |
| $p$-$CH_3O$—$C_6H_4$— | 0.18 | 82 |
| 1-Naphthyl | 0.04 | 72 |

[a] Data from H. M. Walborsky and G. E. Niznik, *J. Org. Chem.*, **37**, *187 (1972). Thionyl chloride was also earlier* reported by Uzi as a means of dehydrating formamides to isonitriles [59] but the foregoing procedure is an improvement.

yield), b.p. 55.5–56.6°C (11 mm), $n_D^{20}$ 1.4178. Infrared spectrum (neat) 2110 $cm^{-1}$ (s); nmr (neat) $\delta$1.08 [s, 9, $C(CH_3)_2$], 1.43 [t, 6, J = 2Hz, $C(CH_3)_2$], 1.58 (t, 2, J = 2.3 Hz, $CH_2$).

Some other isonitriles prepared by this method are shown in Table IX.

## 4. MISCELLANEOUS METHODS

(1) Addition of substituted phosphines and arsines under base-catalyzed conditions in vinyl isonitrile to afford substituted isonitriles [67].

(2) Reductive deoxygenation of isocyanates and isothiocyanates by means of triethyl phosphite to afford the corresponding isonitriles [68].

(3) Deoxygenation of isocyanates by 2-phenyl-3-methyl-1,3,2-oxazaphospholidine to give isonitriles [69].

(4) Reduction of isothiocyanate with triethylphosphine [70], triphenyltin hydride [71], copper [72], or by photolysis [73].

(5) Dehalogenation of isonitrile dichlorides with tertiary phosphines [74].

(6) The conversion of isonitrile dichlorides to diiodide and subsequent dissociation into isonitrile and iodine [75].

(7) The reductive cleavage of monotrifluoromethyl bromodifluoromethylamine with magnesium to afford trifluoromethyl isonitrile [76].

(8) Oxidation of *n*-butylamine–methanol with oxygen catalyzed by cupric chloride [77].

(9) Preparation of alkyl isonitriles by reacting the alkylation products of alkali metal or silver hexacyanoferrates or hexacyanocobaltates with the hydroxides [78], or cyanides [79a,b], of the Group I metals or even by heating [80].

(10) Preparation of ethyl isonitrile by the reaction of ethanolic solutions of hydrogen hexacyanoferrate and hydrogen cyanide at 120°C [78, 81a–e].

(11) Isonitriles from alkyl halides and onium dicyanoargentates [82].

(12) Preparation of isonitrile complexes of palladium [83].

(13) Formation of an isonitrile and a ketone from an $\alpha$-haloamide [84].

(14) Conversion of *N*-*t*-butyl-1-bromocyclohexane carboxamide via reaction with potassium *t*-butoxide at 75°C to afford *t*-butyl isonitrile [84].

(15) Conversion of *N*-*t*-butyl-$\alpha$-bromoisobutyramide to 1-*t*-butyl-3,3-dimethylaziridin-3-one (54%) and the thermal conversion to acetone (12%), *t*-butyl isonitrile (12%) and *N*-*t*-butylmethacrylamide (65%) [85].

(16) Reaction of 2-methylpyridine with dichlorocarbene to form phenyl isonitrile [86].

(17) Treating sodium aldoximes with 1 mole of *p*-toluenesulfonyl chloride at −30°C in ethanol to afford isonitrile–nitrile mixtures [87].

(18) Conversion of *syn*-isomers of *O*-tosyl oximes to give mixtures of nitriles and isonitriles [87, 88a–d].

(19) Formation of 4-chlorophenyl isonitrile from the sodium salt of *N*-(4-chlorophenyl)dichloromethylsulfonamide [89].

(20) $\alpha$-Hydroxy isonitriles from carbonyl compounds and $\alpha$-metallated isonitriles [90].

(21) Formation of isonitriles by Hofmann degradation of $\beta$-arylglycidamides [91a,b].

(22) Reaction of indole with nitrosobenzene to form phenyl isonitrile [92].

(23) Quinazoline 3-oxide is converted by acetic anhydride into 2-isocyanobenzonitrile [93].

(24) Isonitriles by the reaction of sulfinyl amines with chloroform and potassium hydroxide [96].

(25) Isonitriles from monoimines [97].

(26) Reduction of isocyanates to isonitriles [98].

(27) Preparation of benzyl isonitrile by the oxidation of 5-benzylaminotetrazole [99].

(28) Reaction of cyanotrimethylsilane with oxiranes under the catalytic

action of Lewis acids $Pd(CN)_2$, $SnCl_2$ or $Me_3Ga$ affords trimethylsiloxy isonitriles [100].

(29) Preparation of tri(*t*-butoxy)silyl isonitrile [101].

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# CHAPTER 6/AMIDINES

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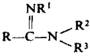
## 1. INTRODUCTION

Amidines having the following structure (I) are described in this chapter,



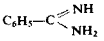
$$\mathrm{R{-}\overset{\overset{NR^1}{\|}}{C}{-}N}\begin{smallmatrix}\mathrm{R^2}\\ \mathrm{R^3}\end{smallmatrix}$$

(I)

where R, $R^1$, $R^2$, and $R^3$, are H, alkyl, aryl, or heterocyclic groups. Amidines where the two nitrogen atoms are part of a heterocyclic ring system are not described in this chapter.

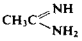
The unsubstituted amidines are basic and react with acids to form crystalline hydrochlorides, sulfates, sulfonates, acetates, nitrates, carbonates, etc.

The nomenclature for the amidines follows the *Chemical Abstracts* system. The amidine is named after the acid or amide that may be obtained from it by hydrolysis. For example, structure (II) is named benzamidine and structure (III) is named acetamidine. Substituents on the nitrogen are designated by *N* and *N′* because the amino or imino nitrogens are not differentiated. (See, however, below.)



$C_6H_5{-}C({=}NH)NH_2$

(II)

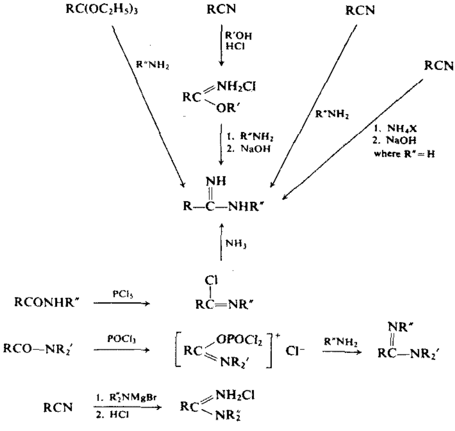


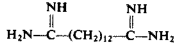
$CH_3C({=}NH)NH_2$

(III)

Amidines have sometimes been designated as carboxamidines when there is a problem in naming these compounds. The two compounds (IV) and (V) illustrate the use of this nomenclature.

SCHEME 1
Methods of Preparation of Amidines

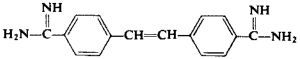




$$H_2N-\overset{NH}{\overset{\|}{C}}-(CH_2)_{12}-\overset{NH}{\overset{\|}{C}}-NH_2$$

**Dodecane-1,12-dicarboxamidine**

(IV)



**Stilbene-4,4′-dicarboxamidine**

(V)

The *1982–1986 Index Guide to Chemical Abstracts* (page 71J) indexes general studies of amidines under the "Amidines" heading. Specific compounds are named as amides of the corresponding imidic acids. For example, the amidine derived from hexanoic acid by replacing the $CO_2H$ group by —C(:NH)$NH_2$ is called "hexanimidamide." Diamidines are named as derivatives of dicarboximidamides. The locants *N* and *N′* denote the amide and imide nitrogen atoms, respectively.

The most important methods for preparing amidines are outlined in Scheme 1.

## 2. ADDITION REACTIONS

The most important addition reaction used for the preparation of amidines is the reaction of nitriles with ammonium salts, amines, and their derivatives. In most cases, the reaction is acid catalyzed. The use of Friedel–Crafts catalysts has been effective in some systems.

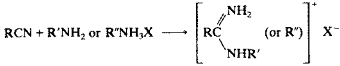
Aromatic nitriles have been found to react with halomagnesium dialkylamides to give *N,N*-disubstituted amidines. This reaction has only limited usefulness with aliphatic nitriles.

### A. Reaction of Nitriles with Ammonia, Amines, and Their Derivatives

Bernthsen [1a,b] first reported that amine hydrochlorides react with certain nitriles to form hydrochlorides. The use of ammonium chloride was not effective. In 1928, Cornell [2] reported that benzamidine and propionamidine were formed in small quantities when the corresponding nitriles were heated with an equimolar mixture of ammonium chloride in ammonia at 200°C. Omitting the ammonium chloride gave no detectable reaction. Krewson and Couch [3] reported that ammonium hydroxide reacts with nicotinitrile to give 73% nicotinamide. Later, Short and co-workers [4a–f] reported on the results of an extensive investigation of the reaction of nitriles with ammonium thiocyanate sulfonates to give amidines. Later, they showed that the presence of free ammonia favored the formation of amidines.

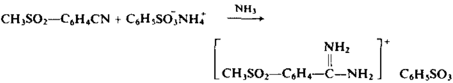
Short and co-workers [5] also showed that no amidine could be isolated by heating nitriles such as *p*-sulfonamidophenyl cyanide at 200–250°C with ammonium chloride, sulfate, phenoxide, picrate, sulfamate, selenate, or diammonium hydrogen phosphate.

Table I summarizes the important reactions of nitriles with amine or amine derivatives to give amidines, according to Eq. 1.



$$\mathrm{RCN} + \mathrm{R'NH_2}\ \text{or}\ \mathrm{R''NH_3X} \longrightarrow \left[\mathrm{RC}\begin{smallmatrix}\nearrow\!\!\!\!\nearrow \mathrm{NH_2} \\ \searrow \mathrm{NHR'}\end{smallmatrix}\quad (\text{or } \mathrm{R''})\right]^{+} \mathrm{X^-} \tag{1}$$

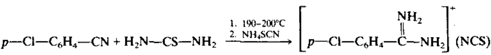
## 2-1. *Preparation of* p-*Methylsulfonylbenzamidinium Benzenesulfonate* [4d]



$$\mathrm{CH_3SO_2{-}C_6H_4CN} + \mathrm{C_6H_5S\overset{-}{O}_3\overset{+}{N}H_4} \xrightarrow{\mathrm{NH_3}} \left[\mathrm{CH_3SO_2{-}C_6H_4{-}}\overset{\overset{\displaystyle \mathrm{NH_2}}{\|}}{\mathrm{C}}\mathrm{{-}NH_2}\right]^{+} \mathrm{C_6H_5SO_3^-} \tag{2}$$

To a flask containing 9.05 gm (0.05 mole) of *p*-methylsulfonylphenyl cyanide is added 8.8 gm (0.05 mole) of ammonium benzenesulfonate. The mixture is heated at 180°C for 2½ hr while a stream of dry ammonia is passed in. The reaction mixture soon solidifies and is extracted with acetone to remove unreacted cyanide (1.45 gm, 16%). The insoluble residue is recrystallized from hot water to afford 14.8 gm (83%), m.p. 253°C.

## 2-2. *Preparation of* p-*Chlorobenzamidine Thiocyanate* [6]



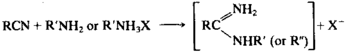
$$p\mathrm{{-}Cl{-}C_6H_4{-}CN} + \mathrm{H_2N{-}CS{-}NH_2} \xrightarrow[\text{2. } \mathrm{NH_4SCN}]{\text{1. 190–200°C}} \left[p\mathrm{{-}Cl{-}C_6H_4{-}}\overset{\overset{\displaystyle \mathrm{NH_2}}{\|}}{\mathrm{C}}\mathrm{{-}NH_2}\right]^{+} \mathrm{(NCS)^-} \tag{3}$$

To a flask is added 5.5 gm (0.04 mole) of *p*-chlorobenzonitrile and 12.2 gm (0.16 mole) of thiourea. The reaction mixture is heated at 190–200°C for 5 hr, cooled, and then extracted with ether to remove the unreacted *p*-chlorobenzonitrile (9%). The insoluble residue is suspended in ice water, and ammonium thiocyanate is added to near saturation to precipitate the amidine thiocyanate. The product is filtered to afford 7.7 gm (90%), m.p. 202–203°C (recrystallized).

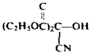
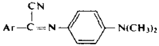
NOTE: In some cases, the product and unreacted ammonium thiocyanate have similar solubilities in water.

# TABLE I

## REACTION OF NITRILES WITH AMINES OR AMINE DERIVATIVES TO GIVE AMIDINES

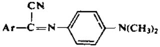


$$RCN + R'NH_2 \text{ or } R'NH_3X \longrightarrow \left[ RC\begin{matrix} \diagup\!\!\!\!= NH_2 \\ \diagdown NHR' \text{ (or } R'') \end{matrix} \right] + X^-$$

| Nitrile (moles) | Amine (moles) | Amine derivative | Solvent (ml) | Reaction conditions | | Yield of amidine (%) | B.p., °C (mm Hg) | $n_D$ (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Temp. (°C) | Time (min) | | | | |
|  $(C_2H_5O\overset{\overset{C}{\|}}{C})_2\underset{\underset{CN}{\mid}}{C}{-}OH$ | $(C_3H_7)_2NH$ | — | Ether<br>(5.0) | −17 | 1 | — | 72.5–73 | — | *k* |
| $C_6H_5CN$<br>(0.66) | $C_6H_5NH_2$[a]<br>(0.67) | — | — | 200 | 30 | 69–74 | 114–115.5 | — | *l* |
| $C_6H_5{-}CN$<br>(0.05) | $C_6H_5NHCH_3$[b]<br>(0.05) | — | — | 160 | 20 | 100 | 85.5 | — | *m* |
| $C_6H_5CN$ | — | $C_6H_5\overset{+}{N}H_3S\overset{-}{O}_3C_6H_5$ | — | 270 | 15 | 81.5 | 173[c] | — | *n* |
| *p*-$CN{-}C_6H_4{-}SO_2CH_3$<br>(1.0) | — | $NH_4SCN$<br>(4.0) | $H_2O$<br>(40) | 100–180 | 45 | 70 | 295[d] | — | *o* |
| *m*-$CN{-}C_6H_4SO_2CH_3$ | — | $NH_4SCN$<br>(4.0) | $H_2O$<br>(40) | 100–180 | 120 | 84 | 184–185[e] | — | *o* |
| $C_6H_5CN$<br>(0.2) | — | $C_6H_5CH_2NHMgBr$<br>(0.2) | Ether<br>(150) | 36 | 10 | 24 | 227–229[d] | — | *p* |
| $CH_3{-}CN$<br>(1.0) | — | $NaNH_2$ (1.1)<br>+ *n*-$C_8H_{17}Br$ (1.0) | — | 45–50 | 360 | 52 | 120<br>(19) | 1.4310<br>(18) | *q* |
| <br>(1.0) | — | $C_6H_5NH_3{}^+Cl^-$<br>(4.0) | $C_6H_5NH_2$<br>(500) | 185 | 4 | 84 | 146 | — | *r* |

*(continues)*

TABLE I (*Continued*)

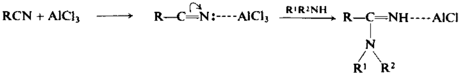
| Nitrile (moles) | Amine (moles) | Amine derivative | Solvent (ml) | Reaction conditions | | Yield of amidine (%) | B.p., °C (mm Hg) | $n_D$ (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Temp. (°C) | Time (min) | | | | |
| <br>(1.0) | — | — | $C_6H_5NH_2$ (500) + $CH_3COOH$ (glacial) (60) | 100 | 60 | 92 | 146 | — | *r* |
| $p$-CN—$CH_2C_6H_4$—$NH_2$[f]<br>(0.033) | — | — | — | 220 | 60 | — | *g* | — | *s* |
| $(CN)_2$<br>(0.5) | $H_2N$—$(CH_2)_4NH_2$<br>(0.5) | — | $C_2H_5OH$<br>(236 gm) | 0–5 | 360 | — | *h* | — | *t* |
| $CF_3CN$<br>(0.18) | $NH_3$<br>(1.0) | — | — | −33 | 60 | 15 | 35–36<br>(11) | 1.3801<br>(25) | *u* |
| $CF_3CF_2CF_2CN$<br>(0.07) | $NH_3$<br>(0.023) | — | — | −78 to 0 | 60 to 1440 | 100[i] | 44.3–44.7<br>(1.5) | — | *v* |
| $p$-Cl—$C_6H_4$—CN<br>(0.04) | — | $H_2N$—CS—$NH_2$<br>(0.16) | — | 190–200 | 300 | 90 | 202–203[j] | — | *w* |

[a] 0.67 mole $AlCl_3$ (anhydrous) is added to the reaction mixture. [b] 0.005 mole $AlCl_3$ (anhydrous) is added to the reaction mixture. [c] Benzenesulfonate salt. [d] Hydrochloride salt. [e] Thiocyanate salt. [f] 0.2 gm $AlCl_3$ (anhydrous) is added to the reaction mixture. [g] Specific viscosity for the polyamidine hydrochloride, 0.64. [h] The light orange polyamidine is thought to have the following structure: $[—(CH_2)_4—NH—C(NH)C(NH)—NH—]_n$. [i] The product is $N'$-(perfluorobutyrimidoyl) perfluorobutyramidine obtained by the thermal condensation of the perfluorobutyramidine. [j] $p$-Chlorobenzamidine thiocyanate. [k] R. S. Curtiss and L. F. Nickell, *J. Amer. Chem. Soc.* 35, 885 (1913). [l] F. C. Cooper and M. W. Partridge, *Org. Syn. Coll.* 4, 769 (1963). [m] P. Oxley, M. W. Partridge, and W. F. Short, *J. Chem. Soc.* 1110 (1947). [n] P. Oxley and W. F. Short, *J. Chem. Soc.* 147 (1946); P. Oxley, M. W. Partridge, and W. F. Short, *ibid.* 303 (1948). [o] M. W. Partridge and W. F. Short, *J. Chem. Soc.* 390 (1947). [p] R. P. Hullin, J. Miller, and W. F. Short, *J. Chem. Soc.* 394 (1947). [q] G. Newberg and W. Webster, *J. Chem. Soc.* 738 (1947); C. J. Eby and C. R. Hauser, *J. Amer. Chem. Soc.* 79, 723 (1957). [r] F. Sachs and E. Bry, *Chem. Ber.* 34 118 (1901); F. Kröhnke and H. H. Steuernagel, *ibid.* 96, 486 (1963). [s] S. O. Kamura and T. Higashimura, Japanese Pat. 9965 (1965); *Chem. Abstr.* 64, 839 (1966). [t] K. Matsuda, U.S. Patent 3,049,499 (1962). [u] W. L. Reilly and H. C. Brown, *J. Amer. Chem. Soc.* 78, 6023 (1956). [v] H. C. Brown and P. D. Schuman, *J. Org. Chem.* 28, 1122 (1963). [w] F.C. Schaefer and A. P. Krapcho, *J. Org. Chem.* 27, 1255 (1962).

Partridge and Short [7] have used ammonium thiocyanate to convert nitriles by a method similar to that described above.

The method of Preparation 2-2 is definitely not as generally useful as that using the ammonium halides in the presence of ammonia, described in Preparation 2-4.

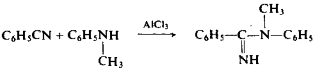
Short and co-workers [4c] reasoned that because nitriles with electron-withdrawing groups react better with ammonia or amines, the use of Lewis acid catalysts such as aluminum chloride might help to activate unsubstituted nitriles toward such reaction (Eq. 4):



$$RCN + AlCl_3 \longrightarrow R{-}C{\equiv}N{:}\cdots AlCl_3 \xrightarrow{R^1R^2NH} R{-}\underset{\substack{|\\ N\\ R^1\ \ R^2}}{C}{=}NH\cdots AlCl_3 \qquad (4)$$

Zinc chloride, ferric chloride, stannic chloride, and triphenyltin chloride are also effective, but boron trifluoride or triphenyl borate are ineffective. This method affords good yields of *N*,*N*-dialkyl amidine and is a useful supplement to the ammonium salt method, as seen in the second and third entries of Table I.

### 2-3. *Preparation of* N-*Phenyl*-N-*methylbenzamidine* [4c]



$$C_6H_5CN + \underset{\substack{|\\ CH_3}}{C_6H_5NH} \xrightarrow{AlCl_3} C_6H_5{-}\underset{\substack{\|\\ NH}}{C}{-}\overset{\substack{CH_3\\ |}}{N}{-}C_6H_5 \qquad (5)$$

To a flask containing a mixture of 5.15 gm (0.05 mole) of benzonitrile and 5.35 gm (0.05 mole) of *N*-methylaniline is added, slowly with stirring, over a 20-min period, 6.7 gm (0.05 mole) of anhydrous powdered aluminum chloride (exothermic reaction). The mixture is kept at 160°C for 20 min and while still molten, is poured slowly into a solution of 2 ml of concentrated hydrochloric acid in 200 ml of water.

**CAUTION:** Hood, face shield, gloves, etc.

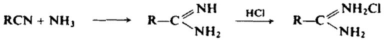
After the addition, about 2.0 gm of activated carbon is added to the solution, and it is filtered hot. The filtrate is poured in a steady stream into a solution prepared from 22.0 gm (0.5 mole) of sodium hydroxide in 100 ml of water. The flocculent precipitate is collected by filtration onto alkali-resistant filter paper, washed with water, air-dried at room temperature to constant weight, and recrystallized from petroleum ether (b.p. 60–80°C) in needles, to afford 10.5 gm (100%) m.p. 85.5°C. The picrate has a melting point of 187°C.

Ogonor [4g] obtained a 62% yield when *p*-tolunitrile was reacted with *N*-methylaniline in the presence of aluminum chloride at 160°C. within 20 min. He also prepared amidines by reacting nitriles with aromatic amines at low temperature in the presence of gaseous hydrogen chloride. In this case, long reaction times were required.

Reilly and Brown [8a,b] found that the strong electronegative effect of the fluorocarbon group in the perfluoronitriles considerably increases its reactivity with ammonia and gives amidines in good yields.

Schaefer and Krapcho reported a simple amidine synthesis involving the reaction of nitriles with ammonium chloride or bromide in the presence of ammonia at 125–150°C in pressure equipment (Eqs. 6, 7) [6].

$$NH_4Cl \longrightarrow NH_3 + HCl \qquad (6)$$



$$RCN + NH_3 \longrightarrow R{-}C\overset{\displaystyle NH}{\underset{\displaystyle NH_2}{\lessgtr}} \xrightarrow{HCl} R{-}C\overset{\displaystyle NH_2Cl}{\underset{\displaystyle NH_2}{\lessgtr}} \qquad (7)$$

Table II lists some representative amidines prepared from various nitriles and either ammonium chloride or bromide. Cornell's earlier procedure was improved as shown in the first entry of Table II.

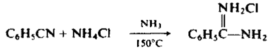
The reaction in Eqs. (6) and (7) is applicable to any nitrile that is not degraded by ammonia at 150°C. Electronegative substituents accelerate the rate. Tolunitrile is unreactive, whereas *o*-chlorobenzonitrile is converted to the amidine hydrobromide at a reasonable rate. Unsubstituted nitriles such as propionitrile are also effective, giving the amidines, contrary to earlier beliefs [4a].

The use of ammonium bromide gives a faster rate in some cases, but ammonium chloride is suitable in most cases.

Methanol and ethanol are useful solvents in this reaction consequently the reaction requires less ammonia. An ammonia:nitrile ratio of 1.2 to 1 is effective.

The incorporation of alcohols in these reaction systems may give rise to the transient or intermediate formation of amidates by reaction of nitrile with an alcohol, which are then subjected to ammonolysis.

### *2-4. Preparation of Benzamidine Hydrochloride* [6]



$$C_6H_5CN + NH_4Cl \xrightarrow[150°C]{NH_3} C_6H_5\overset{\displaystyle NH_2Cl}{\overset{\|}{C}}{-}NH_2 \qquad (8)$$

To a stainless steel rocking autoclave equipped with a stirrer is added 103.0 gm (1.0 mole) of benzonitrile, 214.0 gm (4.0 mole) of ammonium chloride, and 306.0 gm (18.0 mole) of ammonia is introduced by means of

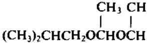
## TABLE II
### PREPARATION OF AMIDINE SALTS

$RCN + NH_4X \rightarrow RC(NH)NH_2 \cdot HX$

| R = | X = | $NH_4X$[a] (moles) | $NH_3$[a] (moles) | Temp.[b] | Yield (%) | M.p. (°C) | Recovered nitrile (%) |
|---|---|---|---|---|---|---|---|
| $C_6H_5$ | $Cl^-$ | 1 | 18 | 200 | 8[c, d] | | |
| | | 4 | 18 | 150 | 77 | 161–163[e] | 5 |
| | | 1 | 2.0[f] | 125 | 81 | 166–168[e] | 10 |
| | $Br^-$ | 4 | 18 | 125 | 75 | 85–110[g] | 5 |
| | | 3 | 18 | 150[h] | 78 | 109–111 | — |
| | | 1 | 1.2 | 155 | 70 | 121–123 | — |
| | $NO_3^-$ | 1 | 22 | 150[i] | 48 | 116–120[j] | 20 |
| $4\text{-}ClC_6H_4$ | $Cl^-$ | 4 | 20 | 125 | 72[k] | 237–239[l] | — |
| | $SCN^-$ | 4 | 20 | 125[m] | *ca.* 50 | 190–195 | — |
| $2\text{-}ClC_6H_4$ | $Br^-$ | 3 | 40 | 125 | 30 | 236–237[n] | 63 |
| $4\text{-}CH_3OC_6H_4$ | $Br^-$ | 2 | 40 | 140 | 48 | *o* | 13 |
| $3\text{-}C_5H_4N$ | $Cl^-$ | 1 | 50 | 125 | 86 | 166–175[p] | 5 |
| $C_2H_5$ | $Br^-$ | 4 | 20 | 150 | 80 | 103–108[q] | — |
| | | 0.8 | 1.2 | 150 | 80 | 100–108 | — |

*(continues)*

TABLE II (*Continued*)

| R = | X = | $NH_4X$[a] (moles) | $NH_3$[a] (moles) | Temp.[b] | Yield (%) | M.p. (°C) | Recovered nitrile (%) |
|---|---|---|---|---|---|---|---|
| *n*-$C_3H_7$ | $Cl^-$ | 4 | 20 | 150 | 55 | 90[r] | — |
|  | $Br^-$ | 4 | 20 | 150 | 83 | 106–110 | — |
| *i*-$C_3H_7$ | $Br^-$ | 4 | 12 | 150 | 54 | [s] | — |
| $C_6H_5CH_2$ | $Cl^-$ | 4 | 22 | 150 | 87 | 145–147[t] | — |
| *t*-$C_4H_9OCH_2$ | $Br^-$ | 2 | 45 | 125[u] | 81 | 128–134[v] | — |
|  $(CH_3)_2CHCH_2O\overset{\overset{CH_3}{\vert}}{C}HO\overset{\overset{CH_3}{\vert}}{C}H$ | $Br^-$ | 2 | 50 | 135[u] | 41 | 116–126[w] | 35 |
| 4-Cyclohexenyl | $Cl^-$ | 4 | 22 | 150 | 53 | 162–163[x] | 16 |

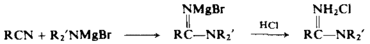
[a] Moles of reagent per equivalent of nitrile. [b] Reaction time 18 hr except as noted. [c] Average of two runs approximating the procedure of Cornell; 12% yield of 180°. [d] Yields based on chloride content of ethanol-soluble fraction. [e] Lit. m.p. 169°. [f] Methanol present; 200 cc/mole RCN. [g] M.p. was 122°–124°C after recrystallization from acetonitrile. *Anal.* Calcd. for $C_7H_3N_2 \cdot HBr$: C, 41.81; H, 4.51; N, 13.94. Found: C, 41.53; H, 4.72; N, 14.16. [h] Reaction time 5 hr. [i] Reaction time 8 hr. [j] Purity 95% by nitrogen analysis. Lit. m.p. 128°. [k] Recovered a 20% yield of 4-chlorobenzamide. [l] Lit. m.p. 241°–242°C. [m] The autoclave was badly corroded and the reaction mixture was a black tarry mass. This was worked up in approximately the way described for the preparation of the amidine thiocyanate using the atmospheric-pressure fusion process. [n] Recrystallized from acetonitrile. *Anal.* Calcd. for $C_7H_8N_2BrCl$: C, 35.70; H, 3.42; N, 11.90. Found: C, 35.77; H, 3.75; N, 11.49. [o] The oily solid obtained gave a purple coloration with aqueous ferric chloride indicative of some demethylation to the phenol. A picrate crystallized from ethanol had m.p. 209°–211°C. Lit. m.p. 212°–213°C. [p] M.p. 189°–190°C after recrystallization from ethanol. Lit. m.p. 192°–194°C. [q] M.p. 112°–114°C after recrystallization from acetonitrile. *Anal.* Calcd. for $C_3H_9N_2$: Br, 52.22, Found: Br, 52.16. [r] Recrystallized m.p. 97°–100°C. Lit. m.p. 94°–96°C. [s] Mushy crystals, 91% pure by bromide analysis. The yield is corrected for this. [t] Lit. m.p. 151°–153°C. [u] Reaction time 4 hr. [v] M.p. 134°–145°C after recrystallization from acetonitrile. [w] Infrared spectrum and water solubility confirm amidine structure. [x] *Anal.* Calcd. for $C_7H_{13}N_2Cl$: Cl, 22.07. Found: Cl, 22.0. [Reprinted from F. C. Schaefer and A. P. Krapcho, *J. Org. Chem.* **27**, 1255 (1962). Copyright 1962 by the American Chemical Society. Reprinted by permission of the copyright owners.]

a transfer bomb. The reaction mixture is heated at 150°C for 18 hr (pressure: 1300–6500 psig), cooled, and, with appropriate precautions for the safe control of the excess ammonia, is vented to atmospheric pressure. The reaction mixture is extracted with ether to remove approximately 5% unreacted benzonitrile, and then extracted with hot acetonitrile or ethanol to separate the amidine hydrochloride from the unreacted ammonium chloride. Concentration of the latter affords 120.5 gm (77%) of benzamidine hydrochloride, m.p. 161–163°C.

NOTE: The use of 200 ml of methanol in this preparation is also effective and reduces the reaction pressures to about 350–400 psig. See Table II for examples of additional amidine hydrochlorides made by a similar method.

Other ammonium salts were evaluated for use in this reaction. Ammonium acetate affords the amide instead of the amidine acetate. Ammonium sulfate and ammonium phosphate are ineffective, probably because of their low solubilities. Ammonium nitrate is effective but is not recommended because of the potential hazard inherent in this reagent. Ammonium thiocyanate is effective at 125°C but causes very serious corrosion of stainless steel equipment.

While Hullin et al. [9] found that the addition of halomagnesium dialkylamides to aliphatic nitriles (Eq. 9) was of limited preparative value, Lorz and Baltzly [10] found that the reaction can be more successfully applied to aromatic nitriles, as seen in Table III.



$$\mathrm{RCN} + \mathrm{R_2'NMgBr} \longrightarrow \overset{\mathrm{NMgBr}}{\overset{\|}{\mathrm{RC}}}\mathrm{{-}NR_2'} \xrightarrow{\mathrm{HCl}} \overset{\mathrm{NH_2Cl}}{\overset{\|}{\mathrm{RC}}}\mathrm{{-}NR_2'} \qquad (9)$$

### 2-5. *General Procedure for the Reaction of Halogenomagnesium Dialkylamides with Nitriles to Prepare* N,N-*Disubstituted Amidines*

*General procedure for the addition reactions.** To a solution of ethylmagnesium bromide containing about 50% excess Grignard reagent (on the basis of the nitrile to be used) is added gradually a slight excess of the secondary amine. Evolution of ethane generally continues for about 30 min. The solution is then refluxed 15–20 min further and the nitrile is added, usually in ethereal solution, but in some cases dissolved in benzene (for reasons of solubility). After the solution has been refluxed for 2–3 hr, or occasionally longer (as indicated in Table III), the reaction mixtures are

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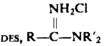
* General procedures adapted from E. Lorz and R. Baltzly, *J. Amer. Chem. Soc.* **70**, 1904 (1948). Copyright 1948 by the American Chemical Society. Reprinted by permission of the copyright owner.

## TABLE III

### PREPARATION OF *N*,*N*-DIALKYLAMIDINE HYDROCHLORIDES, R—C—NR'₂



$$R{-}\overset{\overset{NH_2Cl}{\|}}{C}{-}NR'_2$$

| R = | R' = | Method of isolation[l] | Yield (%) | M.p. (°C) |
|---|---|---|---|---|
| Phenyl | *n*-Butyl | A | 82[a] | 174[b] |
| *o*-Tolyl | *n*-Butyl | A | 70[a] | 192[c] |
| *o*-Methoxyphenyl | *n*-Butyl | B | 45[d, e] | 161 |
| *o*-Chlorophenyl | *n*-Butyl | B | 83[e] | 234 |
| *m*-Chlorophenyl | *n*-Butyl | B | 70[e] | 170 |
| *p*-Chlorophenyl | *n*-Butyl | B | 80[e] | 149 |
| *p*-Dimethylaminophenyl | *n*-Butyl | B | 74[e] | 197 |
| Styryl | *n*-Butyl | C | 55[f] | 204 |
| 1-Naphthyl | *n*-Butyl | B | 72[e] | 211 |
| 2-Methoxy-1-naphthyl | *n*-Butyl | C | 63[d, f] | 196 |
| 9-Acridyl | *n*-Butyl | B | 69[d, e] | 285 (dec.) |
| 4-Tetrahydropyranylmethyl | *n*-Amyl | — | *g* | 128 |
| Phenyl | Benzyl | C | 66[f] | 228 |
| 4-Quinolyl | Ethyl | | *g* | 213.5 (dec.) |
| 4-Quinolyl free base | Ethyl | | *h* | 111 |
| 4-Quinolyl | *n*-Propyl | B | 80[e] | 266 (dec.) |
| 4-Quinolyl | *n*-Butyl | — | *g*, *i* | 214 |
| 4-Quinolyl | *n*-Amyl | — | *g* | 151 (dec.) |
| 4-Quinolyl | *n*-Hexyl | B | 69[e] | 159 |
| 4-Quinolyl | *n*-Heptyl | B | 70[e] | 154–155 |
| 4-Quinolyl | *n*-Octyl | B | 60[e] | 149 |
| Mesityl | *n*-Butyl | B | 72[e,k] | 254–255 |
| *N*-Phenyl-*N*-*n*-butylbenzamidine hydrochloride | — | A | 50[a,j] | 214 |
| 1-Phenyl carbimido-1,2,3,4-tetrahydroquinoline hydrochloride | — | B | 45[e] | 229 (dec.) |
| *N*-Benzyl-*N*'-phenylcarbimidopiperazine dihydrochloride | — | C | 52[f] | 267 (dec.) |

[a] Yield calcd. on weight of distilled base. [b] B.p. of base, 120°–121°C (1 mm Hg). [c] B.p. of base, 140°C (1 mm Hg). [d] The nitrile was dissolved in benzene for addition to the bromomagnesium dialkylamide. [e] Yield calcd. on weight of purified hydrochloride. [f] Yield calcd. on weight of crude base precipitated during hydrolysis of reaction mixture. [g] Obtained as by-product in condensation. [h] Crystallized from ethyl acetate–ether mixture. [i] B.p. of base, 180°–190°C (1 mm Hg). [j] B.p. of base, 172°C (1 mm Hg). [k] After addition of the nitrile the solution was allowed to stand for 16 hr at room temperature and refluxed 5 hr longer. Allowing for recovered cyanomesitylene, the yield was 93%. [l] For methods *A*, *B*, and *C*, see Procedure 2-5. [Adapted from E. Lorz and R. Baltzly, *J. Amer. Chem. Soc.* **70**, 1904 (1948). Copyright 1948 by the American Chemical Society. Reprinted by permission of the copyright owner.]

decomposed with ice and ammonium chloride solution and worked up further, according to three general procedures.

*Method A.* The total material from the hydrolysis of the reaction mixture is made strongly alkaline. The amidine base and remaining secondary amine are taken into ether, dried, and separated by distillation in vacuo. This procedure is preferred for the more volatile amidines.

*Method B.* The material from the hydrolysis of the reaction mixture is steam-distilled, thereby removing unreacted nitrile and secondary amine. It is usually necessary to add some strong alkali in order to ensure volatilization of secondary amine. The residual material is then made strongly alkaline, and the remaining bases are taken into ether. When quite involatile secondary amines are employed (dioctylamine), it is advantageous to extract the ethereal layer with successive inadequate amounts of dilute hydrochloric acid, a separation being thus obtained of stronger from weaker bases. The aqueous extracts are made acid to Congo paper, evaporated separately in vacuo, and the residues are crystallized from suitable solvents.

*Method C.* In certain cases, the amidine base precipitates during the hydrolysis of the reaction mixture with ammonium chloride solution. The bulk of the product is thus filtered off at this stage. It is usually necessary to partition it between dilute sodium hydroxide solution and benzene, in order to free the base of small amounts of magnesium salts. The bases are then acidified with ethanolic hydrogen chloride solution and crystallized as hydrochlorides.

All the amidines reported in Table III recrystallized readily as the hydrochlorides, though seldom in characteristic form. Most of the crystals appeared to be stubby prisms or rhombs. The acridine derivative and the dibenzylbenzamidine are crystallized from absolute ethanol; the piperazine derivative is crystallized from 95% ethanol. All the others are purified by crystallization from ethanol–ether mixtures.

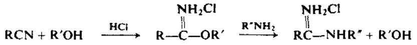
## 3. SUBSTITUTION REACTIONS

The most important substitution reactions used in preparing amidines involve the reaction of amines with imidates, ortho esters, or imidoyl chlorides. The first two involve the displacement of the alkoxy group by an amino group and the latter involves the reaction of an amine with an amide derivative. In the case of dialkyl acetamides or dialkyl formamides, the phosphorus oxychloride derivatives are successfully reacted with amines to give *N*,*N*-dialkyl-*N*′-substituted acetamidines or formamidines.

One procedure involves the use of triethyloxonium fluoroborate to react with amides to give imidate fluoroborate derivatives, which, in turn, give amidines in good yields, upon reaction with amines. This has the advantage that the imidate derivatives are available from the easily obtainable amides rather than the nitriles used in the Pinner synthesis.

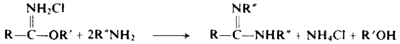
### A. Reaction of Imidates Derived from Nitriles with Ammonia, Amines, and Their Derivatives

Pinner first described the preparation of amidines by the reaction of imidate salts (see Chapter 8) with ammonia or amines in absolute ethanol [11]. The base strength of the amine influences the rate of the reaction. The imidate salts, as described earlier, are prepared (Eq. 10) by passing dry hydrogen chloride into an anhydrous equimolar mixture of a nitrile and an alcohol in ether solution at 0–25°C, where R″ = H, alkyl [11, 12a–e], aryl, aryl $SO_2$ [13a–d]. The amine may be secondary [14a,b] but not tertiary [15a]. In addition, R″ may be R″NH (where R″ = alkyl or aryl) [15b].



$$\mathrm{RCN + R'OH \xrightarrow{HCl} R{-}\overset{\overset{NH_2Cl}{\|}}{C}{-}OR' \xrightarrow{R''NH_2} R\overset{\overset{NH_2Cl}{\|}}{C}{-}NHR'' + R'OH} \qquad (10)$$

*N*-Substituted imidates react with primary amines to give *N,N′*-disubstituted amidines (Eq. 11) [16a,b]. In all cases where acid salts are used, a disproportionation reaction occurs to give a mixture of the symmetrically substituted amidines [17a–c]. *N,N′*-Disubstituted amidines also result when excess primary amine is reacted at elevated temperatures with imidate salts [18a–c].

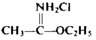
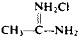
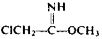
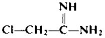
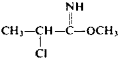
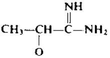
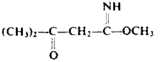
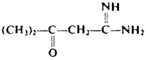
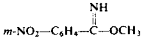
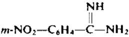
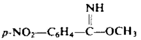
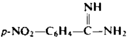
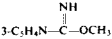
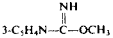
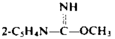
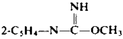
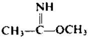
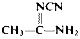
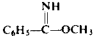
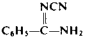


$$\mathrm{R{-}\overset{\overset{NH_2Cl}{\|}}{C}{-}OR' + 2R''NH_2 \longrightarrow R{-}\overset{\overset{NR''}{\|}}{C}{-}NHR'' + NH_4Cl + R'OH} \qquad (11)$$

Many examples of the preparation of amidines by this method are found in the literature. These are outlined briefly in Table IV.

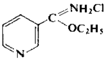
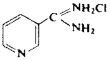
The foregoing method has several limitations. Large volumes of anhydrous solvents are required during the reactions and the starting nitriles are not always readily available. (A more convenient method of preparing imidates from substituted nitriles is described later in this section.) In addition, γ-chloro-α-phenylbutyrimidate hydrochloride cyclizes to 2-imino-3-phenyl-pyrrolidine when treated with ammonia [19]. The method also has no general application to the synthesis of ortho-substituted benzamidines since the imidates are produced in very poor yield. Poor yields of *o*-chlorobenzamidine [19] and 1-naphthamidine [4a] have been reported and *o*-toluamidine has not been made thus far by this method [4a, 19]. Furthermore, *N,N′*-disubstituted amidines cannot be prepared using the Pinner method.

## TABLE IV
### Preparation of Amidines Using Imidates

| Imidate (moles) | $RNH_2$ (moles) | Amidine | Yield (%) | M.p. (°C) | Ref. |
|---|---|---|---|---|---|
|  $CH_3-\overset{\overset{NH_2Cl}{\|}}{C}-OC_2H_5$<br>(2.44) | $NH_3$<br>(2.44) |  $CH_3-\overset{\overset{NH_2Cl}{\|}}{C}-NH_2$ | 80–91 | 164–166 | *a* |
|  $ClCH_2-\overset{\overset{NH}{\|}}{C}-OCH_3$<br>(2.5) | $NH_4Cl$<br>(2.5) |  $Cl-CH_2-\overset{\overset{NH}{\|}}{C}-NH_2$ | 96 | 95–99 | *b* |
|  $CH_3-\underset{\underset{Cl}{\vert}}{CH}-\overset{\overset{NH}{\|}}{C}-OCH_3$<br>(3.1) | $NH_4Cl$<br>(3.1) |  $CH_3-\underset{\underset{O}{\vert}}{CH}-\overset{\overset{NH}{\|}}{C}-NH_2$ | 73 | 130–131 | *b* |
|  $(CH_3)_2-\underset{\underset{O}{\|}}{C}-CH_2-\overset{\overset{NH}{\|}}{C}-OCH_3$<br>(1.0) | $NH_4Cl$<br>(1.0) |  $(CH_3)_2-\underset{\underset{O}{\|}}{C}-CH_2-\overset{\overset{NH}{\|}}{C}-NH_2$ | 78 | 157–159 | *b* |
|  $m\text{-}NO_2-C_6H_4-\overset{\overset{NH}{\|}}{C}-OCH_3$<br>(1.0) | $NH_4Cl$<br>(1.0) |  $m\text{-}NO_2-C_6H_4-\overset{\overset{NH}{\|}}{C}-NH_2$ | 80 | 250–252 | *b* |
|  $p\text{-}NO_2-C_6H_4-\overset{\overset{NH}{\|}}{C}-OCH_3$<br>(0.95) | $NH_4Cl$<br>(0.95) |  $p\text{-}NO_2-C_6H_4-\overset{\overset{NH}{\|}}{C}-NH_2$ | 78 | 285–287 | *b* |
|  $3\text{-}C_5H_4N-\overset{\overset{NH}{\|}}{C}-OCH_3$<br>(1.0) | $NH_4Cl$<br>(1.0) |  $3\text{-}C_5H_4N-\overset{\overset{NH}{\|}}{C}-OCH_3$ | 65 | 192–194 | *b* |
|  $2\text{-}C_5H_4N-\overset{\overset{NH}{\|}}{C}-OCH_3$<br>(1.0) | $NH_4Cl$<br>(1.0) |  $2\text{-}C_5H_4-N-\overset{\overset{NH}{\|}}{C}-OCH_3$ | 95 | 149–151 | *b* |
|  $CH_3-\overset{\overset{NH}{\|}}{C}-OCH_3$<br>(0.1) | $H_2NCN$<br>(0.1) |  $CH_3-\overset{\overset{NCN}{\|}}{C}-NH_2$ | 72 | 135–137 | *c* |
|  $C_6H_5-\overset{\overset{NH}{\|}}{C}-OCH_3$<br>(0.1) | $H_2NCN$<br>(0.1) |  $C_6H_5-\overset{\overset{NCN}{\|}}{C}-NH_2$ | 72 | 142–142.5 | *c* |

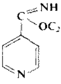
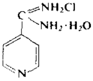
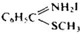
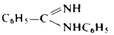
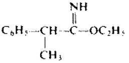
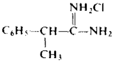
(*continues*)

TABLE IV (*continued*)

| Imidate (moles) | RNH₂ (moles) | Amidine | Yield (%) | M.p. (°C) | Ref. |
|---|---|---|---|---|---|
| $C_2H_5\overset{\overset{NH}{\Vert}}{C}-OCH_3$<br>(0.1) | $H_2N-CN$<br>(0.1) | $C_2H_5-\overset{\overset{NCN}{\Vert}}{C}-NH_2$ | 53 | 78.5–80 | *c* |
| $ClCH_2-\overset{\overset{NH}{\Vert}}{C}-OCH_3$<br>(0.1) | $H_2NCN$<br>(0.1) | $Cl-CH_2-\overset{\overset{NCN}{\Vert}}{C}-NH_2$ | 59 | 110.5–111.5 | *c* |
| $Cl_3C-\overset{\overset{NH}{\Vert}}{C}-OCH_3$<br>(0.1) | $H_2NCN$<br>(0.1) | $Cl_3C-\overset{\overset{NCN}{\Vert}}{C}-NH_2$ | 43 | 166.5–168 | *c* |
| $p\text{-}NO_2-C_6H_5\overset{\overset{NH}{\Vert}}{C}-OCH_3$<br>(0.1) | $H_2NCN$<br>(0.1) | $p\text{-}NO_2-C_6H_5-\overset{\overset{NCN}{\Vert}}{C}-NH_2$ | 52 | 233–234 | *c* |
| $2\text{-}C_5H_4N-\overset{\overset{NH}{\Vert}}{C}-OCH_3$<br>(0.1) | $H_2NCN$<br>(0.1) | $2\text{-}C_5H_4N-\overset{\overset{NCN}{\Vert}}{C}-NH_2$ | 83 | 224–226 | *c* |
| $CH_3-\overset{\overset{NCN}{\Vert}}{C}-OCH_3$<br>(0.043) | $NH_3$<br>(0.088) | $CH_3-\overset{\overset{NCN}{\Vert}}{C}-NH_2$ | 67 | 132–135 | *d* |
| $CH_3-\overset{\overset{NCN}{\Vert}}{C}-OCH_3$<br>(0.0204) | $NH_2C_6H_5$<br>(0.0204) | $CH_3-\overset{\overset{NCN}{\Vert}}{C}-NHC_6H_5$ | 70 | 189.5–192 | *d* |
| $CH_3-\overset{\overset{NH_2Cl}{\Vert}}{C}-NH_2$<br>(1.0) | NaHNCN<br>(1.0) | $CH_3-\overset{\overset{NCN}{\Vert}}{C}-NH_2$ | 63 | 134–136 | *c* |
| $C_6H_5-OCH_2C\begin{matrix}=NH_2Cl\\ \diagdown OC_2H_5\end{matrix}$<br>(0.01) | $NH_3$<br>(0.013) | $C_6H_5OCH_2-\overset{\overset{NH}{\Vert}}{C}-NH_2$ | 72 | 127.5–128.5 | *e* |
| $C_6H_5OCH_2-C\begin{matrix}\diagup NH_2Cl\\ \diagdown OC_2H_5\end{matrix}$<br>(0.01) | $(CH_3)_2NH$<br>(0.013) | $C_6H_5OCH_2-C\begin{matrix}=NH\\ \diagdown N\begin{matrix}\diagup CH_3\\ \diagdown CH_3\end{matrix}\end{matrix}$ | 77 | 187–189 | *e* |
| <br>(0.0296) | $NH_4Cl$<br>(0.0227) |  | 100 | 190 | *f* |

(*continues*)

TABLE IV (*continued*)

| Imidate (moles) | $RNH_2$ (moles) | Amidine | Yield (%) | M.p. (°C) | Ref. |
|---|---|---|---|---|---|
| <br>(0.023) | $NH_4Cl$<br>(0.023) |  | 56 | 246–248 | *g* |
| <br>(0.1) | $C_6H_5NH_2$<br>(0.1) |  | 92 | — | *h* |
|  $C_6H_5-CH(CH_3)-C(=NH)-OC_2H_5$<br>(0.1) | $NH_4Cl$<br>(0.1) |  $C_6H_5-CH(CH_3)-C(=NH_2Cl)-NH_2$ | — | 235 | *i* |

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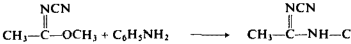
[a] A. W. Dox, *Org. Syn Coll.* **1**, 51 (1941). [b] F. C. Schaefer and G. A. Peters, *J. Org. Chem.* **26**, 412 (1961). [c] K. R. Huffman and F. C. Schaefer, *J. Org. Chem.* **28**, 1812 (1963). [d] K. R. Huffman and F. C. Schaefer, *J. Org. Chem.* **28**, 1816 (1963). [e] C. Djerassi and C. R. Scholz, *J. Amer. Chem. Soc.* **69**, 1688 (1947). [f] H. J. Barber and R. Slack, *J. Amer. Chem. Soc.* **66**, 1607 (1944). [g] E. J. Poziomek, *J. Org. Chem.* **28**, 590 (1963). [h] P. Raynaud, R. C. Moreau, and N. H. Thu, *C. R. Acad. Sci. Paris* **253**, 2540 (1961). [i] R. Delaby, P. Reynaud, and F. Lilly, *C. R. Acad. Sci. Paris* **246**, 2905 (1958).

More recently, [20] it has been reported that substituted nitriles react with alcohols under base-catalyzed conditions to give imidate directly. This method is useful for a wide range of electronegatively substituted aliphatic and aromatic nitriles. Unsubstituted nitriles do not undergo this reaction but can be converted to the imidate by the Pinner method.

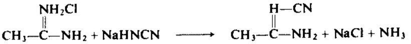
### *3-1. Preparation of* N*-Cyanoacetamidine (Method 1)* [21]



$$CH_3-\overset{\overset{\displaystyle NCN}{\|}}{C}-OCH_3 + C_6H_5NH_2 \longrightarrow CH_3-\overset{\overset{\displaystyle NCN}{\|}}{C}-NH-C_6H_5 \qquad (12)$$

To a flask containing 2.0 gm (0.0204 mole) of methyl *N*-cyanoacetimidate is added 1.9 gm (0.0204 mole) of aniline dissolved in 5.4 ml of ethanol. The reaction mixture is refluxed for 12 hr, chilled, the white crystalline product filtered, washed with ether, and dried to afford 2.25 gm (70%), m.p. 189.5–192°C. Recrystallization from ethanol raised the melting point to 191.5–193.5°C.

### *3-2. Preparation of* N-*Cyanoacetamidine (Method 2)* [22]

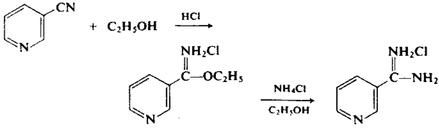


$$CH_3\text{—}\overset{\overset{NH_2Cl}{\|}}{C}\text{—}NH_2 + NaHNCN \longrightarrow CH_3\text{—}\overset{\overset{H\text{—}CN}{\|}}{C}\text{—}NH_2 + NaCl + NH_3 \qquad (13)$$

To a flask containing 94.5 gm (1.0 mole) of acetamidine hydrochloride is added with stirring 69.5 gm (1.0 mole) of 92% monosodium cyanamide [23] in 100 ml of water. After 2-hr stirring, the reaction mixture is cooled, the precipitate is filtered off, and the latter is extracted well with hot acetone. The acetone solution is concentrated to a small volume, cooled, and filtered, to afford 38.5 gm of white crystals, m.p. 134–136°C. The filtrate is further concentrated to afford an additional 6.0 gm of product, m.p. 125–133°C. Concentration of the original aqueous filtrate affords another 7.7 gm, m.p. 125–130°C, for a total yield of 52.2 gm (63%).

NOTE: Monosodium cyanamide is prepared from calcium cyanamide and sodium hydroxide [23].

### *3-3. Preparation of 3-Amidinopyridine* [24a]

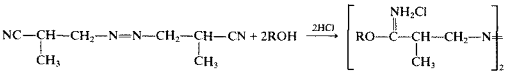


(14)

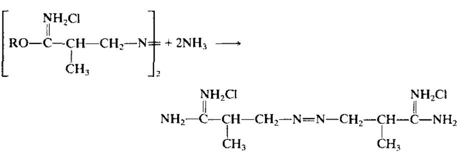
A flask containing 6.0 gm (0.058 mole) of 3-cyanopyridine dissolved in 50 ml of dry chloroform and 3.0 gm (0.065 mole) of absolute ethyl alcohol is cooled to 0°C while dry hydrogen chloride saturates the reaction mixture. The contents are allowed to stand at 0°C for 16 hr and then poured into a separatory funnel containing enough of an ice-cold 50% sodium hydroxide solution to give an alkaline solution. The mixture is shaken vigorously, then the chloroform layer is separated, washed with water until neutral, dried over potassium carbonate, and concentrated to give the crude imidate. The latter is dissolved in 20 ml of 75% aqueous ethanol containing 1.2 gm (0.0224 mole) of ammonium chloride and heated at 70°C for 4 hr, charcoal filtered, and diluted with 2–3 volumes of acetone. The unreacted ammonium chloride that separates is filtered, and the filtrate is again diluted with acetone until the cloud point. After standing for several hours at 0°C, 4 gm (100%), m.p. 190°C, of product separates (colorless needles).

The preparation of 2,2′-azobis isobutyramidine hydrochloride is of interest because this particular compound is a nonoxidizing source of free radicals for emulsion polymerizations in aqueous dispersions.

A solution of 2,2′-azobis-(isobutyronitrile) in methanol or ethanol is treated with gaseous hydrogen chloride at 5°C to form the corresponding imidate. The imidate is washed with cold methanol and then is treated with an excess of anhydrous ammonia in methanol for 16 hr. The reaction mixture is evaporated, at low temperatures, to dryness. After extracting the product with cold water, the aqueous solution is concentrated at low temperatures and then cooled at 3°C to form the crystalline product (Eqs. 14a, 14b) [24a,b,c].



$$NC-\underset{CH_3}{CH}-CH_2-N{=}N-CH_2-\underset{CH_3}{CH}-CN + 2ROH \xrightarrow{2HCl} \left[RO-\overset{NH_2Cl}{\overset{\|}{C}}-\underset{CH_3}{CH}-CH_2-N{=}\right]_2 \qquad (14a)$$



$$\left[RO-\overset{NH_2Cl}{\overset{\|}{C}}-\underset{CH_3}{CH}-CH_2-N{=}\right]_2 + 2NH_3 \longrightarrow NH_2-\overset{NH_2Cl}{\overset{\|}{C}}-\underset{CH_3}{CH}-CH_2-N{=}N-CH_2-\underset{CH_3}{CH}-\overset{NH_2Cl}{\overset{\|}{C}}-NH_2 \qquad (14b)$$

Frequently the amidines are isolated and used as hydrochloride or other salts. The preparation of the free amidine bases appears to be quite straightforward: The amidine hydrochloride is dissolved in dry methanol and treated with an equivalent amount of freshly prepared sodium methylate in methanol. After cooling and filtering the precipitated sodium chloride off, the product solution is concentrated on a rotary evaporator. Then the product is separated by fractional distillation [24d].

Table V lists a number of amidines prepared by the Pinner procedure discussed so far, along with the corresponding free amidine bases.

Treatment of nitriles in alcohol with sodium borohydride also leads to imidate solutions, which are converted to amidine hydrochlorides upon treatment with ammonium chloride [24e].

The preparation of amidines by the Pinner method may make use either of amidate salts with amines or amine derivatives or, if the amine salts are more available by reaction of these salts, with the free bases derived from the imidate salts [24f]. McFarland and Howes outline three procedures for

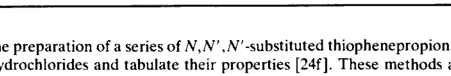
TABLE V

PROPERTIES OF SOME AMIDINE HYDROCHLORIDES AND THE CORRESPONDING FREE BASES [24d]

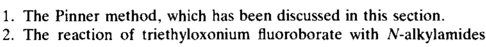
| Compound | M.P. °C | B.P. °C/(mm) | IR Peaks ($cm^{-1}$) |
|---|---|---|---|
| *N,N*-Dimethylacetamidine | | | |
| hydrochloride | 158–159 | — | 1625, 1675 |
| free base | — | 75/(67) | 1595 |
| *N,N*-Dimethylpropionamidine | | | |
| hydrochloride | 184–186 | — | 1625, 1675 |
| free base | — | 61/(28) | 1590 |
| α-Phenyl-*N,N*-dimethylacetamidine | | | |
| hydrochloride | 210–211 | — | 1635, 1685 |
| (free base) | — | 93/(0.2) | 1595 |
| α-Phenylacetamidine (free base) | 62–63 | — | — |

the preparation of a series of *N,N′,N′*-substituted thiophenepropionamide hydrochlorides and tabulate their properties [24f]. These methods are

1. The Pinner method, which has been discussed in this section.
2. The reaction of triethyloxonium fluoroborate with *N*-alkylamides, which is discussed next.
3. The reaction of amides with 1,3-propane sulfone. This method seems to be of limited application. The reaction may be represented by Eqs. 14c and 14d.



(14c)



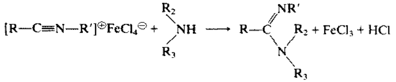
$$Ar{-}CH{=}CH{-}C\begin{matrix}{=}NH_2^{\oplus}\\ \diagdown O(CH_2)_3SO_3^{\ominus}\end{matrix} + (CH_3)_2NH \longrightarrow Ar{-}CH{=}CH{-}C\begin{matrix}{=}NH_2Cl\\ \diagdown N(CH_3)_2\end{matrix}$$

(14d)

Another reaction involving the formation of amidoxime by the addition of hydroxylamine to 2-thiophenepropionitrile is beyond the scope of this chapter.

With ferric chlorides, nitriles are said to form complexes that may be alkylated. The intermediate complexes may be treated with amines to form amidines [24g] (Eqs. 14e, 14f).

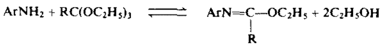
$$\mathrm{RCN + FeCl_3 \xrightarrow{R'Cl} [R{-}C{\equiv}N{-}R]^{\oplus}FeCl_4^{\ominus}} \tag{14e}$$



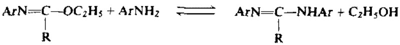
$$\mathrm{[R{-}C{\equiv}N{-}R']^{\oplus}FeCl_4^{\ominus} + R_2R_3NH \longrightarrow R{-}C({=}NR')NR_2R_3 + FeCl_3 + HCl} \tag{14f}$$

## B. Reaction of Amines with Ortho Esters

*N,N'*-Diarylformamidines are formed in good yield by the reaction of ethyl orthoformate and aromatic primary amines (Eqs. 15, 16) [25a–d]. The amidine is formed by reaction of the amine with the initially formed imidate, according to DeWolfe [26a,b].



$$\mathrm{ArNH_2 + RC(OC_2H_5)_3 \rightleftharpoons ArN{=}C(R){-}OC_2H_5 + 2C_2H_5OH} \tag{15}$$

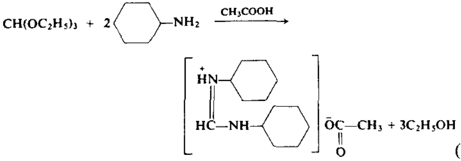


$$\mathrm{ArN{=}C(R){-}OC_2H_5 + ArNH_2 \rightleftharpoons ArN{=}C(R){-}NHAr + C_2H_5OH} \tag{16}$$

Higher orthocarboxylates can also be converted into amidines, but the reaction works best with trialkyl orthoformates to give *N,N'*-disubstituted formamidines, as shown in Tables VI and VII.

The use of a molar equivalent of acetic acid gives good yields of amidines from primary aliphatic and aromatic amines, as shown in Table VI and VII. The use of less than a molar equivalent of acetic acid gives poor yields of amidines and is dramatically illustrated for the case of cyclohexylamine in Table VII. Preparation 3-4 illustrates the technique for the synthesis of *N,N'*-dialkyl amidines using orthoformates.

### *3-4. Preparation of* N,N'*-Dicyclohexylformamidine Acetate* [27]



(17)

TABLE VI

N,N′-DISUBSTITUTED FORMAMIDINES FROM ETHYL ORTHOFORMATE

| Amine | Mole ratio of amine to EOF | Mole ratio of HOAc to EOF | Time (hr) | Product | Yield (%) | M.p. (°C) |
|---|---|---|---|---|---|---|
| $C_6H_{11}NH_2$ | 2 | 1 | 1.25 | $HC(=NC_6H_{11})NHC_6H_{11}$ | $85^b$ | 134–136.5 |
| | 2 | 1/12 | 1.5 | $HC(=NC_6H_{11})NHC_6H_{11}$ | $41^a$ | 106 |
| | 2 | 1/12 | 4.5 | $HC(=NC_6H_{11})NHC_6H_{11}$ | $42^a$ | — |
| | 1 | 1/12 | 1.5 | $HC(=NC_6H_{11})NHC_6H_{11}$ | $49^a$ | — |
| | 2 | 0 | 94 | $HC(=NC_6H_{11})NHC_6H_{11}$ | $15^c$ | — |
| | 2 | 0 | 1.5 | $HC(=NC_6H_{11})NHC_6H_{11}$ | $2.1^c$ | — |
| $C_6H_5CH_2NH_2$ | 2 | 1 | 2 | $HC(=NCH_2C_6H_5)NHCH_2C_6H_5$ | $68^c$ | 76–77 |
| $n$-$C_4H_9NH_2$ | 2 | 1 | 2 | $HC(=NC_4H_9\text{-}n)NHC_4H_9\text{-}n$ | $55^c$ | 117.5–119 |
| $n$-$C_3H_7NH_2$ | 2 | 1 | 1.5 | $HC(=NC_3H_7\text{-}n)NHC_3H_7\text{-}n$ | $62^b$ | b.p. 93°–94° (0.45 mm Hg) |
| $CH_3NH_2$ | 2 | 1 | 1.1 | $HC(=NCH_3)NHCH_3$ | $80^a$ | 116–167.5 |

[a] Isolated as the picrate. [b] Isolated as the acetate by distillation. [c] Isolated as the free amidine. [Adapted from E. C. Taylor and W. A. Ehrhart, *J. Org. Chem.* **28**, 1108 (1963). Copyright 1963 by the American Chemical Society. Reprinted by permission of the copyright owner.]

TABLE VII

REACTION OF AMINES WITH ETHYL ORTHOACETATE (EOA)

| Amine | Amine to EOA (mole ratio) | HOAc to EOA (mole ratio) | Time (hr) | Amidine (%) | Yield ethyl acetimidate (%) | M.p. (°C) |
|---|---|---|---|---|---|---|
| $C_6H_{11}NH_2$ | 2 | 1 | 1.5 | 91[b] | — | 93–95 |
| | 2 | 1/12 | 1.5 | 66[a] | — | 169.5–171.5 |
| | 1 | 1/12 | 2.5 | 60[a] | — | — |
| | 2 | 0 | 94 | 31[a] | — | — |
| | 2 | 0 | 1.5 | 0.5[a] | — | — |
| $C_6H_5CH_2NH_2$ | 2 | 1 | 1 | 73[c] | — | b.p. 202°–211°C (0.75 mm Hg) |
| | 2 | 0 | 7 | 41[c] | — | — |
| $H_2NCH_2CH_2NH_2$ | 1 | 1 | 0.5 | 85[b,d] | — | 94.5–95.5 |
| | 1 | 0 | 94 | 67[c,d] | — | 104–105 |
| $C_6H_5NH_2$ | 2 | 1/12 | 2 | 76[c] | — | 134–135 |
| | 1 | 1/24 | 1.5 | 5.2[c] | 88 | — |
| | 2 | 0 | 1.5 | Trace | 69 | — |
| | 2 | 0 | 4 | 4.6[e] | — | — |
| | 1 | 0 | 1.5 | Trace | 59 | — |
| o-$CH_3OC_6H_4NH_2$ | 2 | 1 | 1.3 | 72[c] | — | 96–97 |
| | 2 | 1/12 | 1.75 | 50[c] | — | — |
| | 1 | 1/12 | 1.5 | 1.7[c] | 87 | — |
| | 0.66 | 0 | 5 | — | 90[f] | — |
| | 2 | 0 | 1.5 | — | 59 | — |
| o-$CH_3C_6H_4NH_2$ | 2 | 1 | 1.5 | 57[c] | — | 69–70.5 |
| o-$ClC_6H_4NH_2$ | 2 | 2/3 | 1.5 | 30[c] | — | 94.5–95.5 |
| p-$NO_2C_6H_4NH_2$ | 2[g] | 1 | 1.25 | 25[c] | — | 262–264 |
| | 2[g] | 0 | 1.25 | — | Trace | — |

[a] Isolated as the picrate. [b] Isolated as the acetate. [c] Isolated as the free amidine. [d] 2-Methyl-$\Delta^2$-imidazoline. [e] Rockwell reported an 83% yield of the amidine under these conditions. [f] This experiment was a repetition and confirmation of an experiment carried out by Rockwell. [g] One mole of pyridine was added. [Adapted from E. C. Taylor and W. A. Ehrhart, *J. Org. Chem.* **28**, 1108 (1963). Copyright 1963 by The American Chemical Society. Reprinted by permission of the copyright owner.]

To a refluxing mixture of 74.0 gm (0.50 mole) of ethyl orthoformate and 30.0 gm (0.50 mole) of glacial acetic acid is added dropwise over a 30-min period 99.0 gm (1.0 mole) of cyclohexylamine. After the addition, the reaction mixture is refluxed for 45 min, and then distilled to remove the volatiles. The residue is cooled to room temperature and held overnight at

0.5 mm. The next day the crystalline mass is filtered to afford 132 gm (99%). Recrystallization from 6/4 cyclohexane/benzene gave an 86% recovery of material, m.p. 134–136.5°C.

NOTE: The free formamidine can be obtained by shaking the product with aqueous sodium carbonate, extracting with ether, drying, concentrating, and recrystallizing from petroleum ether, b.p. 60–70°C, to give white crystals, m.p. 102–104°C.

The reaction of Preparation 3-4 is applicable to aromatic amines (Table VII) and aliphatic primary amines (Table VI). Heterocyclic amines [28a,b], amides [29], ureas [30], hydrazines [31], hydrazides [32], and sulfonamide [33] have also been converted into amidines under the appropriate reaction conditions.

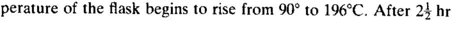
Bredereck has questioned the structure of the products formed from triethyl orthoformate and a number of carboxamides [34].

The reaction of Preparation 3-4 is completed by distilling the alcohol produced, and the yields are usually very good. Aromatic amines with electron-withdrawing groups are more easily converted to formamidines than those with electron-donating groups [35]. The reaction is usually acid-catalyzed. However, the reaction can also take place at a slower rate without added catalysts because the glass surface and other impurities provide small amounts of acid. Most of the *N,N'*-diarylformamidines are crystalline solids, which melt in the range of 100–250°C.

Sterically hindered aromatic primary amines react with triethyl orthoformate to give *N*-arylformimidate esters [26a,b].

Primary aliphatic amines are more basic than the corresponding aromatic counterparts and thus react at a slower rate with triethyl orthoformate. The reaction rate can be accelerated by adding acidic agents such as acetic acid [27] or boron trifluoride etherate [36]. The procedure is limited to amines that boil higher than ethanol. Similar results are achieved by heating an amine acetate [37a,b] or ammonium chloride derivatives [38] with triethyl orthoesters (see Table VIII).

### 3-5. *Preparation of* N,N'*-Diphenylacetamidine* [26a]



$$CH_3C(OC_2H_5)_3 + 2C_6H_5NH_2 \xrightarrow{\text{PTSA}} CH_3\overset{\overset{\displaystyle N-C_6H_5}{\|}}{C}-NH-C_6H_5 + 3C_2H_5OH \qquad (18)$$

A 100-ml round-bottomed flask containing 32.4 gm (0.20 mole) of ethyl orthoacetate, 37.2 gm (0.40 mole) of aniline, and 0.10 gm of *p*-toluenesulfonic acid monohydrate is heated to cause the ethanol to distill rapidly. After a short while, the distillation of ethanol slows down, and the temperature of the flask begins to rise from 90° to 196°C. After 2½ hr, no

## TABLE VIII

### PREPARATION OF AMIDINES FROM ORTHO ESTERS

| | | Reaction | | | | |
|---|---|---|---|---|---|---|
| $RNH_2$ (moles) | $RC(OR)_3$ (moles) | Temp. (°C) | Time (hr) | Yield amidine (%) | M.p. (°C) | Ref. |
| $C_6H_5NH_2$<br>(0.4) | $CH_3C{-}(OC_2H_5)_3$<br>(0.2)<br>*Catalyst: PTSA, 0.006 gm* | 78–196<br>170 | 2½<br>18 | 72[a] | 134.5–136 | *b* |
| $NH_4OAc$<br>(0.20)<br>+ ammonia<br>gas bubbled in | $CH(OC_2H_5)_3$<br>(0.32) | 130–135 | 3/4 | 84 | Acetamidine acetate<br>189–191 | *c* |
| *o*-$(CH_3O)C_6H_4NH_2$ | $CH(OC_2H_5)_3$ | 140 | — | | 105 | *d* |
| *p*-Br—$C_6H_4NH_2$ | $CH(OC_2H_5)_3$ | 100 | — | | 170 | *d* |
| *p*-$(CH_3)_2N{-}C_6H_4NH_2$<br>(2.0) | $CH(OC_2H_5)_3$<br>(1.0) | 125 | 2 | | 157<br>(from $C_6H_6$) | *e* |
| *o*-Cl—$C_6H_4NH_2$<br>(1.4) | $CH(OC_2H_5)_3$<br>(0.7) | 145<br>180 | 1½<br>3½ | 81 | 139–141 | *f* |
| *m*-$NO_2{-}C_6H_4NH_2$<br>(0.025) | $CH(OC_2H_5)_3$<br>(0.025)<br>Solvent: xylene, 50 ml | — | — | 69 | 165–166 | *g* |

[a] Flash distillation of the reaction mixture at 0.001 mm Hg affords 13.6 gm of a distillate consisting of a mixture of aniline and ethyl *N*-phenylacetamidate. The crude *N,N′*-diphenylacetamidine remains in the flask as a residue. Recrystallization affords a 63% yield.

[b] R. H. DeWolfe, *J. Org. Chem.* **27**, 490 (1962).

[c] E. C. Taylor and W. A. Ehrhart, *J. Amer. Chem. Soc.* **82**, 3138 (1960).

[d] F. B. Dains and E. W. Brown, *J. Amer. Chem. Soc.* **31**, 1148 (1909).

[e] F. B. Dains, O. O. Malleis, and J. T. Meyers, *J. Amer. Chem. Soc.* **35**, 970 (1913).

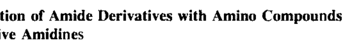
[f] R. M. Roberts, *J. Org. Chem.* **14**, 277 (1949).

[g] R. H. Baker, J. G. Van Oot, S. W. Tinsley, Jr., D. Butler, and B. Riegel, *J. Amer. Chem. Soc.* **71**, 3060 (1949).

more ethanol distills, and the reaction mixture is kept overnight at 107°C. The reaction mixture is flash-distilled to afford 13.6 gm of a mixture of aniline and ethyl *N*-phenylacetimidate. The solid residue is recrystallized from aqueous ethanol to afford 26.4 gm (63%) of colorless crystals, m.p. 134.5–136°C.

## C. Reaction of Amide Derivatives with Amino Compounds to Give Amidines

*N*-Substituted and *N*,*N*′-disubstituted amidines have been prepared by several procedures that involve the reaction of amines with imidoyl chlorides (Eq. 19), either preformed or obtained in situ by reaction secondary and tertiary amides with $PCl_5$ [39a–f], $POCl_3$, $SOCl_2$, or $COCl_2$ [40]. Several examples of this method are described in Table IX.

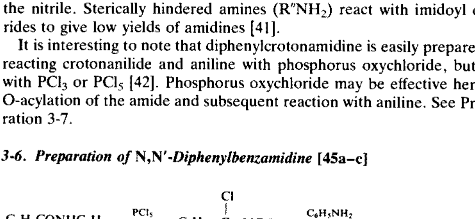


$$\mathrm{RCONHR'} \xrightarrow{\mathrm{PCl_5}} \mathrm{R{-}\overset{\overset{Cl}{|}}{C}{=}NR'} \xrightarrow{\mathrm{R''NH_2}} \mathrm{R\overset{\overset{NHR''}{|}}{C}{=}NR' + HCl} \qquad (19)$$

The use of this method to give amidines has the important advantage that amides are more easily available than the corresponding nitriles. The extension of this method to primary amides is not satisfactory because low yields are obtained, probably because the imidoyl chloride is converted to the nitrile. Sterically hindered amines ($R''NH_2$) react with imidoyl chlorides to give low yields of amidines [41].

It is interesting to note that diphenylcrotonamidine is easily prepared by reacting crotonanilide and aniline with phosphorus oxychloride, but not with $PCl_3$ or $PCl_5$ [42]. Phosphorus oxychloride may be effective here by O-acylation of the amide and subsequent reaction with aniline. See Preparation 3-7.

### 3-6. *Preparation of* N,N′*-Diphenylbenzamidine* [45a–c]

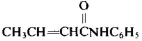
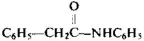


$$\mathrm{C_6H_5CONHC_6H_5} \xrightarrow{\mathrm{PCl_5}} \mathrm{C_6H_5{-}\overset{\overset{Cl}{|}}{C}{=}NC_6H_5} \xrightarrow[\text{pyridine}]{\mathrm{C_6H_5NH_2}} \mathrm{C_6H_5{-}\overset{\overset{\overset{+}{N}HC_6H_5\ Cl^-}{\|}}{C}{-}NHC_6H_5 + pyridine{\cdot}HCl} \qquad (20)$$

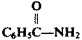
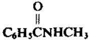
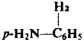
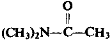
$$\xrightarrow{\mathrm{NH_4OH}} \mathrm{C_6H_5\overset{\overset{N-C_6H_5}{\|}}{C}{-}NHC_6H_5}$$

## TABLE IX

Reaction of Amide Derivatives with Amino Compounds

| Amide | Phosphorus halide (moles) | Other halides (moles) | Amine (moles) | Solvent | Reaction conditions | | Yield (%) | | M.p. (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Temp. (°C) | Time (hr) | Amidine (free) | Amidine (HCl) | | |
| $C_6H_5CONHC_6H_5$<br>(0.46) | $PCl_5$<br>(0.46) | — | Aniline<br>(0.46) | Pyridine<br>(0.46) | 110 | 1/2 | — | — | — | |
| | | | | | 160 | 1½ | | | | |
| | | | | | 160 | 1/3 | 73–80 | — | 144–145 | *a* |
|  $CH_3CH{=}CH\overset{\overset{O}{\Vert}}{C}NHC_6H_5$<br>(0.0285) | $POCl_3$<br>(0.197) | — | Aniline<br>(0.0237) | — | — | — | — | — | 85 | *b* |
| $RCONHC_6H_4{-}OC_2H_5$, R = | | | | | | | | | | |
| $CH_3$–<br>(0.056) | $PCl_5$<br>(0.06) | — | Ethyl-*p*-aminobenzoate<br>(0.05) | $C_6H_6$<br>50 ml | 100 | 3 | 98 | — | 142 | *c* |
| $C_2H_5$–<br>(0.052) | $PCl_5$<br>(0.05) | — | Ethyl-*p*-aminobenzoate<br>(0.05) | 50 ml | 100 | 3 | 93 | — | 146 | *c* |
| $CH_3$–<br>(0.056) | $PCl_3$<br>(0.056) | — | $(C_2H_5)_2NH$<br>(0.056) | 33 gm | 100 | 5 | 24 | — | 119–120 | *d* |
| $C_3H_7CONH_2$<br>(0.0575) | $POCl_3$<br>(0.046) | — | $C_6H_5NH_2$<br>(0.03) | — | 140–150 | 6 | 16 | — | 64–65 | *e* |
|  $C_6H_5{-}CH_2\overset{\overset{O}{\Vert}}{C}{-}NHC_6H_5$<br>(0.015) | $PCl_5$<br>(0.016) | — | $C_6H_5NH_2$<br>(0.03) | — | 100 | 1/20 | — | — | 91 | *f* |

*(continues)*

| Amide | Phosphorus halide (moles) | Other halides (moles) | Amine (moles) | Solvent | Reaction conditions | | Yield (%) | | M.p. (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Temp. (°C) | Time (hr) | Amidine (free) | Amidine (HCl) | | |
| $C_6H_5\text{—NH}\overset{O}{\overset{\|}{C}}H$ (0.092) | $C_6H_5SO_2Cl$ (0.1) | — | $C_6H_5NH_2$ (0.1) | — | 95 | 1/2 | — | Diphenylformamidine | — | *g* |
|  $C_6H_5\overset{O}{\overset{\|}{C}}\text{—}NH_2$ (0.1) | — | $(C_2H_5)_3\overset{+}{O}BF_4^-$ (0.1) | $NH_3$ (0.1) | $CH_2Cl_2$ 250 ml | 25 | 18 | — | 71.5 | 166–168 | *h* |
|  $C_6H_5\overset{O}{\overset{\|}{C}}NHCH_3$ (0.1) | — | $(C_2H_5)_3\overset{+}{O}BF_4^-$ (0.1) | $CH_3NH_2$ (0.14) | 250 ml | 25 | 18 | — | 90 | 255–256 | *h* |
| $(CH_3)_2N\overset{O}{\overset{\|}{C}}H$ (0.5) | PCOl$_3$ (0.25) | — |  $p\text{-}H_2N\text{—}\overset{H_2}{\overset{\vert}{C_6H_5}}$ (0.125) | $C_6H_6$ 160 ml | 60–70 | 7 | 70 | — | 120.5–121.5 | *i* |
|  $(CH_3)_2N\text{—}\overset{O}{\overset{\|}{C}}\text{—}CH_3$ (0.376) | $POCl_3$ (0.15) | — | $C_6H_5NH_2$ (0.125) | 150 ml | 65–70 | 6 | 58 | — | b.p. 75–76°C (0.005) $n_D^{20}$ 1.5775 | *j* |

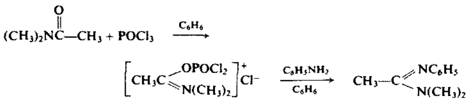
---

[a] A. C. Hontz and E. C. Wagner, *Org. Syn. Coll.* **4**, 383 (1963). [b] M. M. Sidiki and R. C. Shah, *J. Univ. Bombay* 6, Pt. II, 132 (1937). [c] A. J. Hill and M. V. Cox, *J. Amer. Chem. Soc.* 48, 3214 (1926). [d] A. J. Hill and I. Rabinowitz, *J. Amer. Chem. Soc.* **48**, 732 (1926). [e] N. S. Drozdov and A. F. Bekhli, *J. Gen. Chem. (USSR)* 14, 472 (1944). [f] H. Stephen and W. Bleloch, *J. Chem. Soc.* 886 (1931). [g] P. Oxley, D. A. Peak, and W. F. Short, British Pat. 577,478 (1946). [h] L. Weintraub, S. R. Oles, and N. Kalish, *J. Org. Chem.* **33**, 1679 (1968). [i] H. Bredereck and K. Bredereck, *Chem. Ber.* **94**, 2278 (1961). [j] H. Bredereck, R. Gompper, K. Klemm, and H. Rampfer, *Chem. Ber.* **92**, 837 (1959).

To a three-necked, round-bottomed flask equipped with a mechanical stirrer, dropping funnel, and condenser is added 90.0 gm (0.46 mole) of pure dry benzanilide (see Note a) and 95 gm (0.46 mole) of phosphorus pentachloride (see Note b). The mixture is stirred to reduce the lumps and then heated for $\frac{1}{2}$ hr at 110°C and $1\frac{1}{2}$ hr at 160°C, or until the evolution of hydrogen chloride ceases. Then 36.4 gm (0.46 mole) of KOH-dried pyridine (see Note c) is added with stirring, followed by 42.4 gm (0.46 mole) of freshly distilled aniline. The reaction mixture is heated at 160°C for about 20 min to discharge the red color, cooled to about 90°C, and 250 ml of water is added dropwise to precipitate the product in granular form. The product is filtered and added to 500 ml of 28% aqueous ammonia. The mixture is stirred while gently warming for 1 hr, filtered, dried, and recrystallized from 80% ethanol (8–10 ml/gm product) to afford 73–80% product, m.p. 144–145°C.

NOTES: (a) The benzanilide is prepared by reacting aniline and benzoyl chloride in the presence of 10% sodium hydroxide by the Schotten-Baumann procedure. The product is ready for use after recrystallizing it from 95% ethanol. (b) The use of less phosphorus pentachloride or the use of phosphorus oxychloride in place of $PCl_5$ gave poor results. (c) The use of pyridine is not absolutely essential but it helps to make the workup procedure easier.

### *3-7. Preparation of* N,N-*Dimethyl*-N′-*phenylacetamidine* [46a]

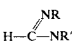


(21)

To a round-bottomed flask equipped with a mechanical stirrer, dropping funnel, and condenser with a drying tube is added 32.7 gm (0.376 mole) of dimethylacetamide in 50 ml of dry benzene. While vigorously stirring 23.1 gm (0.152 mole) of phosphorus oxychloride in 50 ml of benzene is added dropwise at such a rate as to keep the temperature at 20–25°C. The reaction mixture is allowed to stand for 18 hr, at which time a yellow oil separates. The yellow oil is suspended in the reaction medium by vigorously stirring, and then 11.6 gm (0.125 mole) of aniline previously dissolved in 50 ml of benzene is added dropwise, keeping the temperature at 35°C. After 6–7 hr stirring at 65–70°C, the difficult-to-filter product is washed by decantation with benzene. The hydrochloride is added to a separatory funnel containing 100 ml of distilled water and 100 ml of benzene. Then a cold solution 2*N* NaOH is added until the aqueous solution is basic to litmus. The reaction mixture is shaken and the free amidine extracted into benzene. The benzene is separated, and the basic aqueous solution is extracted twice with 100 ml portions of fresh benzene. The combined benzene extracts are dried over potassium carbonate, concentrated under reduced pressure. The residue is distilled using a 30 cm Vigreux column, to afford 11.8 gm (68%), b.p. 75–77°C (0.005 mm Hg), $n_D^{20}$ 1.5775.

By a similar procedure, using chloroform as the solvent for the reaction of aromatic amides with phosphorus oxychloride, *N*,*N'*-bis(2,6-dimethylphenyl)acetamidine was prepared (m.p. of base: 144–145°C) (crystallized from diethyl ether), hydrochloride salt: m.p. 291–293°C. (from acetone). By similar procedures, *N*-methyl-*N'*-2,6-dichlorophenylacetamidine (m.p. free base 91–96°) (hexane) and *N*-methyl-*N'*-2,6-dimethylphenyl acetamidine hydrochloride (m.p. of salt 215–217°C) (methanol/ether) were prepared [46b].

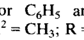
Formamidines of structure



$\mathrm{H{-}C({=}NR){-}N(R')R^2}$

**VI**

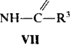
where $R = 2,4\text{-}CH_3(Cl)C_6H_3$ or $C_6H_5$ and $R' = R^2 = CH_3$; $R = 2,4\text{-}Cl_2C_6H_3$ and $R' = CH_2SCH_3$, $R^2 = CH_3$; $R = 2\text{-}CH_3C_6H_4$ and $R' = C_2H_5$, $R^2 = H$; were prepared by reacting an amide of structure



$\mathrm{RNH{-}C({=}O){-}R^3}$

**VII**

where $R^3 = CH_3$ or $CH_2Cl$, with an dialkyl formamide of structure **VIII**

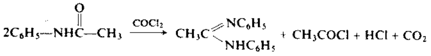


$\mathrm{H{-}C({=}O){-}N(R')R^2}$

**VIII**

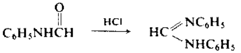
in the presence of thionyl chloride, phosphorus oxychloride, or phosphorus pentachloride, either without any solvent or in solvents such as toluene, chlorobenzene, or xylene [46c].

Phosgene also reacts with 2 moles of acetanilide to give *N,N'*-diphenylacetamidine (Eq. 22) [43].

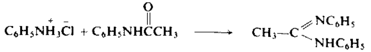


$$2C_6H_5{-}NH\overset{\overset{\displaystyle O}{\|}}{C}{-}CH_3 \xrightarrow{COCl_2} CH_3C\genfrac{}{}{0pt}{}{\nearrow NC_6H_5}{\searrow NHC_6H_5} + CH_3COCl + HCl + CO_2 \qquad (22)$$

In addition, it has been reported earlier that the reaction of hydrogen chloride gas at 100°C with substituted amides also affords amidines (Eqs. 23, 24) [44a,b].



$$C_6H_5NH\overset{\overset{\displaystyle O}{\|}}{C}H \xrightarrow{HCl} HC\genfrac{}{}{0pt}{}{\nearrow NC_6H_5}{\searrow NHC_6H_5} \qquad (23)$$



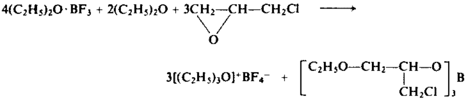
$$C_6H_5\overset{+}{N}H_3\overset{-}{Cl} + C_6H_5NH\overset{\overset{\displaystyle O}{\|}}{C}CH_3 \longrightarrow CH_3{-}C\genfrac{}{}{0pt}{}{\nearrow NC_6H_5}{\searrow NHC_6H_5} \qquad (24)$$

Weintraub et al. [47] found that a superior method of forming amidines by the O-alkylation of amides made use of triethyloxonium fluoroborate (Eq. 25) rather than the phosphorus–halogen compounds. The crude imidate fluoroborates react directly in absolute ethanol to give amidines (Eq. 26). The yields were high in both steps. When *N,N'*-dimethylbenzamidine hydrochloride was prepared by older methods without isolation of the imidate methosulfate, the overall yield was 15%, whereas the yield was 90% using the triethyloxonium fluoroborate method.

The imidate fluoroborates are crystalline solids and are considerably more stable than triethyloxonium fluoroborate.

Reaction (Eq. 26) has one disadvantage: the reagent triethyloxium tetrafluoroborate [48a,b] is not as readily available as phosphorus oxychloride [46], ethyl chloroformate [49], or dimethyl sulfate [50a,b] for the O-alkylation of amides. An example of this method is given in Preparation 3-8, and additional examples will be found in Tables IX, X, and XI.

### *3-8. General Procedure for the Preparation of Amidines by the Reaction of Amines with Imidate Tetrafluoroborates* [47]

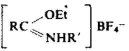


$$4(C_2H_5)_2O\cdot BF_3 + 2(C_2H_5)_2O + 3\underset{\diagdown\,O\,\diagup}{CH_2{-}CH}{-}CH_2Cl \longrightarrow$$

$$3[(C_2H_5)_3O]^+BF_4^- + \left[\begin{matrix}C_2H_5O{-}CH_2{-}\underset{\displaystyle CH_2Cl}{\underset{|}{C}H}{-}O\end{matrix}\right]_3 B \qquad (25)$$

## TABLE X

### IMIDATE FLUOROBORATES



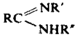
$\left[ RC \overset{\displaystyle OE\dot{t}}{\underset{\displaystyle NHR'}{\lessgtr}} \right] BF_4^-$

| R = | R′ = | Yield (%) | M.p. (°C) |
|---|---|---|---|
| $C_6H_5$ | H | 80.6[a] | 130–131 |
| *o*-$CH_3C_6H_5$ | H | 80.1 | 93–94 |
| 1-Naphthyl | H | 97 | 88–89 |
| *o*-$C_2H_5OC_6H_5$ | H | 90[b] | 139–141 |
| *o*-$ClC_6H_5$ | H | 78 | 101.5–103 |
| $CH_3$ | H | *c* | — |
| $C_6H_5$ | $CH_3$ | 90.1 | 73–74 |

[a] Most of the product precipitated from the $CH_2Cl_2$ solution during the reaction. [b] The starting *o*-ethoxybenzamide was soluble in $CH_2Cl_2$. [c] The crude imidate was converted into the amidine without isolation. Triethyloxonium fluoroborate was added to acetamide below 5°C and the mixture was allowed to warm to room temperature overnight. The solvent was removed completely *in vacuo* and the residue was treated with absolute alcoholic ammonia. [See Table XI for source of this table.]

## TABLE XI

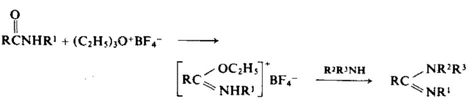
### PREPARATION OF AMIDINES FROM IMIDATE FLUOROBORATES



$RC \overset{\displaystyle NR'}{\underset{\displaystyle NHR''}{\lessgtr}}$

| R = | R′ = | R″ = | Yield (%) | M.p. (°C) Base | M.p. (°C) HCl | M.p. (°C) Picrate |
|---|---|---|---|---|---|---|
| $C_6H_5$ | H | H | 71.5[a] | — | 166–168[b] | — |
| *o*-$CH_3C_6H_5$ | H | H | 90[c] | 104–105[d,e] | 258–258.5[f] | 235–236[g] |
| 1-Naphthyl | H | H | 75[c] | 153–154.5[b,h] | — | 226.5[b] |
| *o*-$C_2H_6OC_6H_5$ | H | H | 91[a] | — | 195–196[i,j] | 213–215[k] |
| *o*-$ClC_6H_5$ | H | H | 90[a] | — | 280–282[l] | 218–220[m] |
| $CH_3$ | H | H | 78[n] | — | — | 249–251[b] |
| $C_6H_5$ | $CH_3$ | $CH_3$ | 90[a] | — | 255–256[b] | 171–172[b] |

[a] Calculated as the hydrochloride. [b] Value agrees with literature. [c] Calculated as the free base. [d] Purified by sublimation at 80°C (0.5 mm). [e] Calculated for $C_8H_{10}N_2$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.58; H, 7.50; N, 20.81. [f] Calculated for $C_8H_{11}N_2Cl$: C, 56.31; H, 6.50; N, 16.42. Found: C, 56.51; H, 6.48; N, 16.54. [g] Calculated for $C_{14}H_{13}N_5O_7$: C, 46.28; H, 3.61; N, 19.28. Found: C, 46.43; H, 3.70; N, 19.37. [h] Sublimed at 130°C (0.5 mm). [i] Melting point reported by A. Pinner [*Chem. Ber.* **23,** 2942 (1890)] is 218°C. [j] Calculated for $C_9H_{13}ClN_2O$: C, 53.87; H, 6.53; N, 13.96. Found: C, 54.15; H, 6.82; N, 13.47. [k] Calculated for $C_{15}H_{15}N_5O_8$: C, 45.81; H, 3.84; N, 17.80. Found: C, 45.84; H, 4.05; N. 17.75. [l] Calculated for $C_7H_8N_2Cl_2$: C, 44.01; H, 4.22; N, 14.66. Found: C. 44.13; H, 4.35; N, 14.63. [m] Calculated for $C_{13}H_{10}N_5O_7Cl$: C, 40.69; H, 2.63; N, 18.25. Found: C, 41.21; H, 278; N. 18.21. [n] Overall yield of amidine picrate based on acetamide. [Tables X and XI are adapted from J. Weintraub, S. R. Oles, and N. Kalish, *J. Org. Chem.* **33,** 1679 (1968). Copyright 1968 by the American Chemical Society. Reprinted by permission of the copyright owners.]



(26)

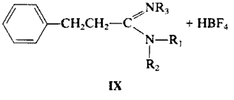
(*a*) *Preparation of triethyloxonium fluoroborate* [48b]. To an oven-dried, 2-liter flask equipped with a mechanical stirrer, dropping funnel, and condenser with drying tube is added in the presence of a dry nitrogen gas stream, 500 ml of ether (sodium-dried) and 284 gm (252 ml, 2.0 moles) of freshly distilled boron trifluoride etherate ($d_4^{25}$ 1.125). From a dropping funnel is added 140 gm (119 ml, 1.51 moles) of freshly distilled epichlorophydrin ($d_4^{25}$ 1.179) at such a rate as to maintain constant reflux (approx. 1 hr). The mixture is refluxed for 1 hr and allowed to stand overnight at room temperature, and then the supernatant ether is removed by means of a filter stick, leaving behind a crystalline mass of triethyloxonium fluoroborate. The crystals are washed three times with 500 ml portions of ether and the ether removed by suction using the filter stick. The crystals are dried by passing dry nitrogen over them and then bottling them in a stream of dry nitrogen to afford 244–272 gm (85–94%), m.p. 91–92°C (dec.). The crystals should be stored at 0–5°C and should be used in a few days. If prolonged storage is desired the compound should be stored under ether or at −80°C.

(*b*) *Preparation of the imidate tetrafluoroborates.* To 0.1 mole of a suspension of amide in 200 ml of dry methylene chloride at room temperature is added dropwise over a 5-min period a solution of 0.1 mole of triethyloxonium fluoroborate in 50 ml of dry methylene chloride. The mixture is stirred for about 18 hr at room temperature or until a clear solution results. The solution is concentrated under reduced pressure to one-third its volume and treated with 5 volumes of ether to precipitate the imidate fluoroborate. The latter is filtered and then redissolved in methylene chloride for step (c). (See also Table X for examples of isolated salts.)

(*c*) *Preparation of amidines.* The crude imidate fluoroborate salt in methylene chloride is treated with a 40% excess of an 8–9% solution of ammonia or methylamine in absolute ethanol. The entire operation is done under strictly anhydrous conditions. After 3 days, the mixture is concentrated under reduced pressure to dryness, treated with a small amount of water, made strongly basic with 5*N* NaOH, and the resulting insoluble oil extracted into ether or ethyl acetate. The crude oil is obtained by concentration of the organic solvent, purified by crystallization, or it is converted to hydrochloride and picrate derivatives. (See Table X for specific examples of the amidines made by this procedure.)

Some examples of important preparative methods are given in Table XI. A brief outline of the experimental reaction conditions is indicated in Table X. The references in Table XI should be consulted for more detailed information.

It should be pointed out the Weintraub et al. procedure is particularly useful for the preparation of *N'*-substituted amidines. Among amidines prepared by this method are those of structure IX [24e].



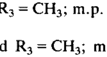
**IX**

where $R_1 = CH_3$, $R_2H$, and $R_3 = CH_3$; m.p. 137–139°C (recrystallized from $CH_3OH/(i\text{-}C_3H_7)_2O$)

$R_1 = C_2H_5$, $R_2 = H$, and $R_3 = CH_3$; m.p. 153–155°C (recrystallized from acetone)

$R_1 = CH_3$, $R_2 = CH_3$, and $R_3 = CH_3$; m.p. 209–211°C (recrystallized from water/methanol)

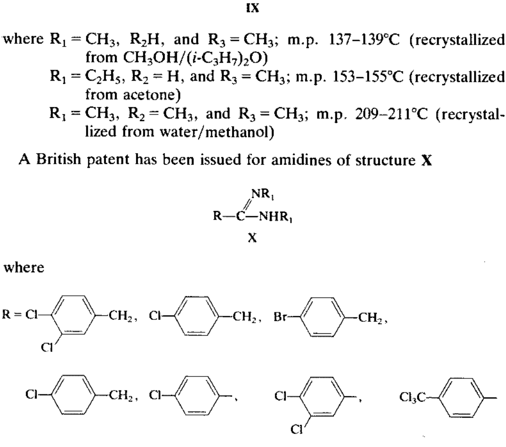
A British patent has been issued for amidines of structure **X**



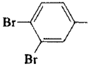
$$R-\overset{\displaystyle NR_1}{\overset{\|}{C}}-NHR_1$$

X

where



or



and $R_1 = CH_3$, $C_2H_5$ or $C_3H_7$ (50c).

*N*-Alkylamidines have also been prepared by heating amides with hexamethylphosphoramide (HMPA) in the presence of morpholine [50d]. While this method appears to be an attractive one, HMPA is considered to be a highly carcinogenic solvent. Therefore, the reader is warned against considering the use of this procedure even with the most stringent safety precautions. The same comment applies to the preparation of amidines from ketoximes with HMPA at high temperatures [50e]. Unfortunately, HMPA is too hazardous for further consideration in modern chemical technology. Even the disposal of reaction mixtures containing residues of the stable, nonvolatile HMPA presents serious problems.

There are also preparations of *N*,*N*′-diphenylformamidines based on treatment of aromatic amides with substituted formamides [50f]. The formamide-type solvents also are beginning to be thought of as possible cancer-suspect agents. We therefore suggest that formamide derivatives should also be handled with great caution.

## 4. MISCELLANEOUS METHODS

(1) Amine exchange in amidines. The reaction of *N*-phenylbenzamidine with cyclohexylammonium chloride to give a mixture of *N*-phenyl- and *N*-cyclohexylbenzamidinium chloride [4e].

(2) Preparation of amidine sulfonates from carboxylic acids and sulfonamides [51].

(3) Preparation of amidoximes [$RC(=NOH)NH_2$] by various methods [24e, 52].

(4) Preparation of *N*,*N*,*N*′-trifluoroamidines by the dehydrofluorination of 1,1-bis(difluoroamino)alkanes or the direct fluorination of fluoroalkylamidines [53].

(5) Preparation of amidines by the sodium borohydride reduction of 1,3-disubstituted ureas [54].

(6) Preparation of bis(perfluoroalkyl)imidoylamidines by reacting perfluoroalkyl monoamidines with perfluoroalkyl dinitriles at 23–24°C [55].

(7) Preparation of acetamidine hydrochloride by the reduction of acetamide oxime with hydrogen and nickel catalyst [56].

(8) Reaction of primary amines with *s*-triazine to give *N*,*N*′-disubstituted formamidine [57].

(9) Reaction of dimethylformamide, dimethyl, and diethyl acetals with compounds containing the primary amino group to give *N*,*N*-dimethyl-*N*′-substituted formamidines [58a–c].

(10) Reaction of *N,N*-dimethylbenzamide dimethyl acetal with amides and sulfonamides to form substituted benzamidines [59].

(11) Reaction of 2-nitro-4-methoxyformanilide with ethyl iodide and silver oxide to afford 2,2′-dinitro-4,4′-dimethoxydiphenylformamidine in 22% yield [60].

(12) Rearrangement of aldehyde arylhydrazones to amidines by heating in xylene with catalytic amounts of sodium amide [61a,b].

(13) Preparation of sulfenylamidines [62].

(14) Reaction of ketoxime sulfonates with ammonia or amines to give substituted amidines [63].

(15) Reaction of *N,N′*-disubstituted thioamide methyl iodide salts with ammonia or primary amines to give aromatic amidines [64].

(16) Reaction of α-hetero-substituted phosphonate carbanions with *C*-nitroso compounds to give amidines [65].

(17) Reaction of isothioureas with amines [66].

(18) Catalytic reduction of amidoximes to amidines [67].

(19) Preparation of amidine salts [68].

(20) Amidines from the reaction of ammonium or substituted ammonium salts with *N*-acyl benzenesulfonalkylamides or acyl benzenesulfonanilides [69].

(21) Reaction of phenyl benzyl ketoxime with thionyl chloride gives diphenylphenacetamidine in low yields. Acetyl chloride, hydrogen chloride, or phosphorus pentachloride may be used in place of thionyl chloride [70].

(22) Preparation of *N,N′*-diphenylbutyramidine by the reaction of butyric acid, aniline, and phosphorus oxychloride [71].

(23) Reaction of *N,N*-diethyl-1,2,2-trichlorovinylamine with aniline to give the corresponding amidine [72].

(24) Preparation of *N,N′*-diphenylbenzamidine by the reaction of diphenylcarbodiimide with phenylmagnesium bromide [73].

(25) Reaction of unsubstituted aromatic of aliphatic thioamides with concentrated ammonium hydroxide–$HgCl_2$ to give amidines [1a, 74].

(26) Reaction of benzoic acid with benzenesulfonamide at 225°C, to give benzamide benzenesulfonate salt [75].

(27) Reaction of Schiff bases with sodium amide in the presence of dry toluene at 120°C [76].

(28) Reaction of phenylcyanamide with Grignard reagents [73].

(29) Preparation of *N,N′*-diphenylformamidine by the reaction of aniline and formic acid in the presence of boric acid or a borate and/or iron [77].

(30) Reaction of diaryl and dialkyl ureas with acid chlorides [78a,b].

(31) Preparation of amidines from trichloroethylene and aromatic amines [79a,b]

(32) Preparation of amidines by the reaction of amines with *N*-alkyl thioamides [1a].

(33) Reaction of *S*-alkyl isothioanilides with amines to give amidines [80a,b].

(34) Reaction of *N*-benzylbenzaldoxime with phenyl isocyanate to give *N*-phenyl-*N*'-benzylbenzamidine [81].

(35) Reaction of Schiff bases with alkyl hypochlorites. For example, *N*,*N*'-diphenylbenzamidine is made by the reaction of *t*-amyl hypochlorite with benzaniline in carbon tetrachloride solution [82].

(36) Preparation of aminoamidine hydrochloride by the reaction of dichloroacetylene with primary amines but not with secondary amines [83].

(37) Oxidation of alkylidene bis arylamines by potassium permanganate in acetone to give *sym*-diaryl formamidines [84].

(38) Preparation of symmetrically substituted amidines by the condensation of β-aminoanthraquinone with carbon tetrachloride and other aromatic hydrocarbons [85].

(39) Reaction of dibenzylcyanamide with alkyl or aryl magnesium bromides and subsequent hydrolysis to give amidines in 75% yields [86].

(40) Reaction of acetanilide with phosphorus pentachloride to give a trisubstituted amidine in 50% yields [87].

(41) Alkylation of amidines by reaction with alkyl halides [88a–d].

(42) Preparation of benzamidine hydrochloride by heating 2,4,6-triphenyltriazine with hydrochloric and acetic acids at 120°C [89a,b].

(43) Condensation of an arylamine with acetanilides by means of phosphorus pentoxide to give amidines [90].

(44) Reaction of ethyl *N*-phenyl formimidate with carboxylic acids and sulfonic acids in alcohol solution to form mono or diacid salts of *N*,*N*'-diphenylformamidine [91].

(45) Preparation of free trisubstituted amidines by the reaction of tetrakis(dimethylamino)titanium with *N*-monosubstituted carboxamides [92].

(46) Preparation of trisubstituted amidines by the reaction of aryloxy acetonitriles with methylamine and hydrogen sulfide [93].

(47) Preparation of amidines by the reaction of dichlorocarbene with imines to give *gem*-dichloroaziridines and subsequent reaction of the latter with amines [94a,b].

(48) Preparation of glycocyamidines [95].

(49) Preparation of cyclic amidines by heating diamines such as (1,3-diaminocyclohexyl)methane with long-chain carboxylic acids such as 12-hydroxystearic acid [96].

(50) Preparation of amidines from carboxylic acids and aromatic amines, using polyphosphoric acid-trimethylsilyl ester as condensing agent [97, 98].

(51) Formation of *N*-(silylmethyl)amidines by reaction of *N*-(trimethylsilyl)methylcarbodiimides with metalloorganic compounds such as aryl or alkyl lithiums in THF or ether [99].

(52) Formamidine preparation by reaction of phenyl isocyanate with dimethylformamide [100].

(53) Formation of *N*,*N*-dialkyl-*N*′-*p*-toluenesulfonylamidines by reaction of *N*,*N*-dialkylamides with *p*-toluenesulfonyl isocyanate [101].

(54) Preparation of *Z*-isomers of amidines by reaction of isocyanides with secondary amines at 0°C, using silver chloride as catalyst. At higher temperatures the *Z*-form isomerizes to the more stable *E*-isomer [102].

(55) Preparation of allene amidines from aminoacetylene derivatives [103].

(56) Preparation of *N*-methyl substituted amidines from *N*-methyl nitrilium fluorosulfates [104].

(57) The preparation of *N*,*N*-substituted amidines and bisamidines by various routes. A review of the relationship of chemical structure and potential antileukemic activity [105].

(58) The formation of amidines in low yield, upon treatment of amidoximes with benzenesulfonyl chloride in pyridine [106].

(59) The preparation of amidines by treatment of aromatic thioureas with sulfones [107].

(60) The preparation of (p-amidinophenyl)methanesulfonyl fluoride, a serine protease inhibitor [108].

(61) Preparation of amidines by the condensation of (chloroalkylene)ammonium chloride with primary or secondary amines in the presence of bases [109].

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# CHAPTER 7/IMIDES

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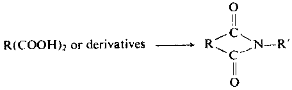
## 1. INTRODUCTION

This chapter covers mainly the methods of synthesis of the monocyclic carboxylic imides derived from dicarboxylic acid derivatives (Eq. 1).



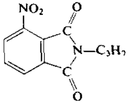
$$\mathrm{R(COOH)_2}\text{ or derivatives} \longrightarrow \mathrm{R}\begin{array}{c}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\\ \\ \underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}\end{array}\mathrm{N{-}R'} \qquad (1)$$

Brief mention will only be made of the acyclic imides and *N*-haloimides [1a–c]. Compounds such as uric acid, alloxan, and barbiturates will not be covered.

The aliphatic imides have earlier been reviewed [2]. The cyclic carboxylic monoimides have also been reviewed [3a]. Among recent reviews are one by Raimahajan and co-workers (in Portugese) [3b] and one by Koehler [3c]. The latter describes the use of imides in the synthesis of heterocyclic nitrogen compounds. In 1987, an interdisciplinary symposium on recent advances in polymeric imides was held in Reno, Nevada. Proceedings of this meeting may become available in due course [3d].

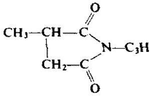
The nomenclature of the imides is derived from the common name of the parent acids for cyclic imides with less than seven atoms. Higher-numbered systems follow the IUPAC nomenclature. Substituents on nitrogen are denoted by the prefix *N*. For other substituents in imides derived from aliphatic acids the numbering starts from one of the carbonyl groups taken as 1.

In the aromatic series the 1-position is taken at the point of attachment of the carbonyl group to the ring. For example,



*N*-Propyl-2-nitrophthalimide

(A)



*N*-Propyl-2-methylsuccinimide

(B)

Most cyclic imides are solids, and the melting points of a representative group are shown in Tables I and II.

The cyclic imides find use as pharmacological agents [4a–c], plant growth stimulators [5], fungicides [6], herbicides, [7], detergents [8], brightening agents [9], vulcanizing agents [10], lubricants [11], solvents [12], and a class of important polymers useful for structural materials, films, and adhesives for high-temperature applications [13a–j]. From polyhalogenated aromatic anhydrides, fire retardant imides may be prepared.

Some of the best synthetic methods for preparing cyclic imides are outlined in Scheme 1.

## 2. CONDENSATION REACTIONS

As described in Scheme 1, the most common condensation methods for the preparation of imides involve the reaction of either the acid or the anhydride with ammonia or an ammonia derivative (ammonium carbonate [14], urea [15], thiourea [16], formamide [17], sulfamic acid [18], ethanolamine [19], dicyandiamide [20], nitriles [21], dicyanide [22], or sodium azide [23]). The use of the acid halide is not recommended and this method has only limited value. An example is found in the Miscellaneous Methods

## TABLE I

MELTING POINTS OF IMIDES[a]

| Compound | M.p. (°C) | Compound | M.p. (°C) |
|---|---|---|---|
| Succinimide | 125–126 | 3-Ethyl-3-methyl-1,2-cyclopropanedicarboximide | 61–63 |
| Methylsuccinimide | 66 | Cyclobutanedicarboximide | 121 |
| 2,2-Dimethylsuccinimide | 105–107 | Cyclopentane-1,2-dicarboximide | 90 |
| *cis*-2,3-Dimethylsuccinimide | 78 | Cyclopentane-1,1-diacetic acid imide | 153–154 |
| *trans*-2,3-Dimethylsuccinimide | 106 | Cyclohexanespirosuccinimide | 145 |
| 2,2-Dimethyl-3-methylsuccinimide | 121 | Cyclohexane-1,2-dicarboximide | 132 |
| Tetramethylsuccinimide | 197 | Cyclohexa-2-ene-1,2-dicarboximide | 173 |
| 2,3-Diphenylsuccinimide | 196–198 | *trans*-Cyclohexa-4-ene-1,2-dicarboximide | 232–233 |
| Tartrimide | 205 | Phthalimide | 241 |
| Malimide | 96 | 1,2-Naphthalimide | 224 |
| Glutarimide | 163–165 | 2,3-Naphthalimide | 275 |
| Carbobenzoxy-2-aminoglutarimide | 122–124 | 1,8-Naphthalimide | 299–300 |
| 3-Methylglutarimide | 142–143 | 4-Nitro-1,8-naphthalimide | 289–290 |
| 3,3-Dimethylglutarimide | 147 | 4-Bromo-1,8-naphthalimide | 296–297 |
| 3,3-Diethylglutarimide | 146–147 | 4-Chloro-1,8-naphthalimide | 302–303 |
| 3-Ethylglutarimide | 87 | 4,5-Dichloro-1,8-naphthalimide | 372–373 |
| Adipimide | 166 | 4-Bromo-5-chloro-1,8-naphthalimide | 365 |
| Maleimide | 93 | 4,5-Dibromo-1,8-naphthalimide | 343–344 |
| Dimethylmaleimide | 118–119 | Anthracene-1,8-dicarboximide | 293–294 |
| Diphenylmaleimide | 213 | Phenanthrene-8,9-dicarboximide | 308–309 |

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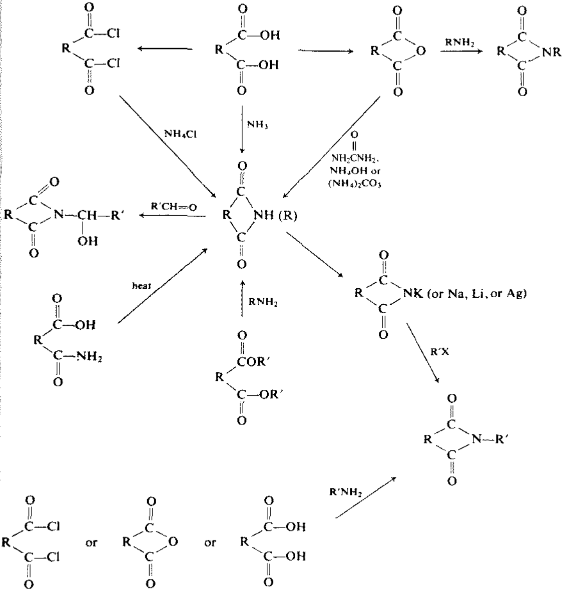
## TABLE II

MELTING POINTS AND BOILING POINTS AT ATMOSPHERIC PRESSURE FOR N-SUBSTITUTED IMIDES[a]

| Compound | M.p. (°C) | B.p. (°C) | Compound | M.p. (°C) | B.p. (°C) |
|---|---|---|---|---|---|
| *N*-Methylsuccinimide | 71 | 226 | *N*-Ethylmaleimide | 45.5 | — |
| *N*-Phenylsuccinimide | 158 | — | *N*-Phenylmaleimide | 90–91 | — |
| *N*-Benzylsuccinimide | 104 | — | *N*-Methyl-2,3-dimethylglutaconimide | 91.5–92.5 | — |
| *N*-Hydroxysuccinimide | 175 | — | *N*-Phenylmalonimide | 246 | — |
| *N*-(Cyanomethyl)succinimide | 121 | — | *N*-Phenylmaleisoimide | 60 | — |
| *N*-Benzoylsuccinimide | 129–130 | — | *N*-Phenylphthalisoimide | 112 | — |
| (+)-*N*-Phenyltartrimide | 257 | — | *N*-Phenylcyclobutanedicarboximide | 89 | — |
| *m*-*N*-Phenyltartrimide | 235 | — | *N*-Methylphthalimide | 136 | — |
| *N*-Benzyltartrimide | 196 | 327 | *N*-Methylphthalimide | 79 | — |
| *N*-Methyltartrimide | 178 | 327 | *N*-Phenylphthalimide | 212 | — |
| *N*-Ethyltartrimide | 174 | 327 | *N*-Benzylphthalimide | 118 | — |
| *N*-Methylglutarimide | 128 | 113.5 | *N*-Vinylphthalimide | 85–86 | — |
|  |  | (20 mm) | *N*-Hydroxyphthalimide | 232–233 | — |
| *N*-Ethylglutarimide | 179–180 | 250–260 | *N*-Benzyloxynaphthalimide | 187–188 | — |
| *N*-Phenylglutarimide | 144–145 | — | *N*-Hydroxynaphthalimide | 280–281 | — |
| *N*-Methyladipimide | 119 | — | *N*-Phenyldiphenyl-1,1′-dicarboximide | 199 | — |
| *N*-Methylmaleimide | 109 | — | Di-*N*-phenyl-*cis*-*cis*-1,2,4,5- |  |  |
| *N*-Methylmaleimide | 90–92 | — | cyclohexanetetracarboximide | 98 | — |

[a] [Reprinted from M. K. Hargraves, J. G. Pritchard, and H. R. Dave, *Chem. Rev.* 70, 439 (1970). Copyright 1970 by the American Chemical Society. Reprinted by permission of the copyright owner.]

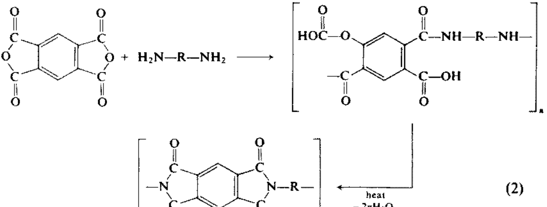
SCHEME 1
The Preparation of Imides



section. Heating the acid and the amine may involve intermediate anhydride formation, amine salt, or monoamide formation before condensation of the imide. Substituents on the aliphatic or aromatic acids [24a,b] do not interfere in this cyclization reaction. Other methods of interest involve the condensation of diesters, monoamides of dicarboxylic acids, or unsubstituted imides to give either imides or substituted imides, as described in a later section.

## A. Condensation of Anhydrides with Ammonia or Its Derivatives

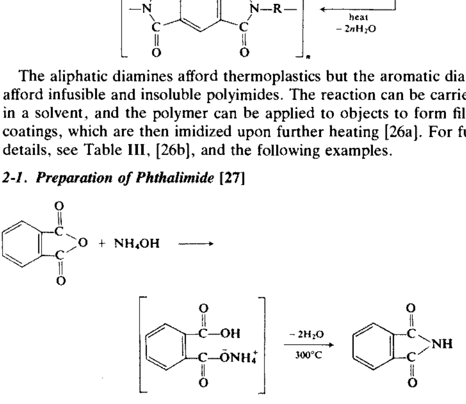
Anhydrides react with ammonia or ammonia derivatives to give imides in good yields, as shown in Table III. The use of diamines and dianhydrides affords polyimides in good yield. For example, pyromellitic dianhydride reacts with a primary diamine as shown in Eq. 2 [25].



(2)

The aliphatic diamines afford thermoplastics but the aromatic diamines afford infusible and insoluble polyimides. The reaction can be carried out in a solvent, and the polymer can be applied to objects to form films or coatings, which are then imidized upon further heating [26a]. For further details, see Table III, [26b], and the following examples.

### *2-1. Preparation of Phthalimide* [27]

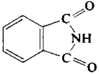
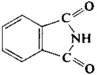
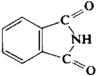
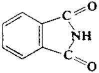


(3)

To a resin kettle fitted with an air condenser and mechanical stirrer and containing 100 gm (0.68 mole) or phthalic anhydride is added 80 gm (89 ml, 1.3 moles) of a 28% aqueous ammonia solution. The water is removed by slowly heating. Then the temperature is raised to 300°C. The sublimate in the condenser is pushed back into the reaction mixture. After

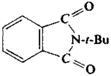
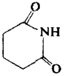
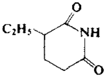
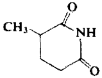
## TABLE III

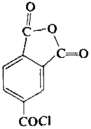
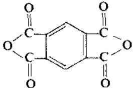
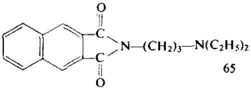
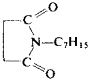
### PREPARATION OF IMIDES FROM ANHYDRIDES AND AMMONIA, AMINES, OR AMINE DERIVATIVES

| Anhydride (moles) | $RNH_2$ (moles) | Reaction conditions | | Structure of imide | Yield imide (%) | M.p. (°C) | Ref. |
|---|---|---|---|---|---|---|---|
| | | Temp. (°C) | Time (hr) | | | | |
| Phthalic<br>(3.4) | (28%) $NH_4OH$<br>(6.6) | 100<br>300 | 1<br>2 |  | 95–97 | 232–235 | *a* |
| (3.4) | $(NH_4)_2CO_3$<br>(4.4) | 300 | 2 |  | 95–97 | 232–235 | *a* |
| (0.67) | $NH_3$<br>(2.0) | 160 | 2 |  | — | — | *b* |
| (0.108) | Dicyandiamide<br>(0.036) | 300 | 3 |  | 80.5 | 231–232 | *c* |
| (2.0) | Dicyandiamide<br>(3.0) | 300 | 3 | | 90.7 | 231–232 | |

(*continues*)

TABLE III (*Continued*)

| Anhydride (moles) | $RNH_2$ (moles) | Reaction conditions Temp. (°C) | Reaction conditions Time (hr) | Structure of imide | Yield imide (%) | M.p. (°C) | Ref. |
|---|---|---|---|---|---|---|---|
| (0.67) | *t*-Butylurea<br>(0.3) | 200<br>240 | 1/6<br>1/12 |  | 76 | 59–60 | *d* |
| Glutaric<br>(0.15) | $NH_3$<br>(0.5) | 130–140<br>250 | 1/2<br>1/2 |  | — | 163–165 | *e* |
| α-Ethylglutaric<br>(0.15) | $NH_3$<br>(0.5) | 130–140<br>250 | 1/2<br>1/2 |  | 85 | 107–108 | *e* |
| α-Methylglutaric<br>(0.11) | $NH_3$<br>(0.5) | 120<br>200 | 1/2<br>1/2 |  | 100 | 91 | *f* |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
|  | $R(NH_2)_2$ | 50–330 | 1–2 | Polyimides–polyamides | 90–100 | — | g |
|  | $Ar(NH_2)_2$ | −20 to 70 | 1–2 | Polyimide | — | — | h |
| Naphthalic<br>(0.152) | $(C_2H_5)_2N—CH_2CH_2CH_2NH_2$<br>(0.152) | 165 | 1 |  | 65<br>(hydrochloride) | 226–227 | i |
| Succinic<br>(0.25) | $n\text{-}C_7H_{15}NH_2$<br>(0.25) | 100<br>160–170 | 18<br>2 |  | 67 | b.p.<br>111°–114°C (0.5) | j |

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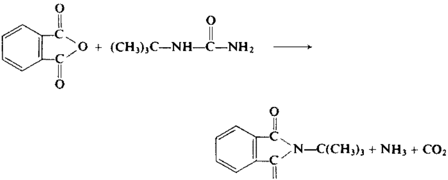
[a] W. A. Noyes and P. K. Porter, *Org. Syn. Coll.* **1**, 457 (1941). [b] G. W. Pucher and T. B. Johnson, *J. Amer. Chem. Soc.* **44**, 817 (1922). [c] M. T. Dangyan, *Bull. Arm. Branch Acad. Sci. USSR* No. 9/10 (23/24) 53–72 (1942). [d] L. I. Smith and O. H. Emerson, *J. Amer. Chem. Soc.* **67**, 1862 (1945); L. I. Smith and O. H. Emerson, *Org. Syn. Coll.* **3**, 151 (1955); R. H. F. Manske, *J. Amer. Chem. Soc.* **51**, 1202 (1929); J. B. Tingee and B. F. P. Brenton, *J. Amer. Chem. Soc.* **32**, 113 (1910). [e] K. W. Doak and A. H. Corwin, *J. Amer. Chem. Soc.* **71**, 159 (1949). [f] W. W. Crouch and H. L. Lochte, *J. Amer. Chem. Soc.* **71**, 159 (1949). [g] S. R. Sandler, F. R. Berg, and G. Kitazawa, U.S. Pat. 3,531,436 (1970). [h] G. M. Bower and L. W. Frost, *J. Polym. Sci.* **1**, 3135 (1963). [i] A. M. Mattocks and O. S. Hutchison, *J. Amer. Chem. Soc.* **70**, 3474 (1948). [j] L. M. Rice, E. E. Reid, and C. H. Grogan, *J. Org. Chem.* **19**, 884 (1954).

1 hr the crude product is poured out into a Pyrex dish, cooled, and weighed to give 94–96 gm (95–97%) of phthalimide (m.p. 238°).

NOTES: (a) Powdered ammonium carbonate or urea can be used in place of aqueous ammonia. (b) Phthalimide may be recrystallized from water. Solubility, 4 gm/liter water at 25°C.

### 2-2. *Preparation of N-t-Butylphthalimide* [28]

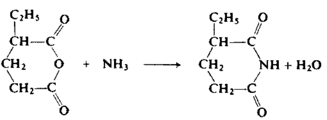


(4)

To a 1-liter flask equipped with a condenser is added an intimate mixture of 35 gm (0.30 mole of *t*-butylurea [29] and 100 gm (0.67 mole) of phthalic anhydride. The flask is immediately placed in an oil bath at 200°C and after about 10 min, when the initial vigorous effervescence subsides, the temperature is rapidly raised to 240°C and maintained there for 5 min. The product is cooled, 100 ml of ethanol is added, and the mixture is made alkaline with aqueous sodium carbonate. The mixture is diluted to 1 liter with water, filtered, and the solid pressed dry on filter paper and then heated with 500 ml of b.p. 60–68°C petroleum ether. The hot petroleum ether is filtered, dried, and concentrated to one-third of its volume, cooled, and filtered to give 43.5 gm of product. The remaining filtrate is concentrated, cooled, and filtered to give 3.0 gm of product. Both product fractions melt at 59–60°C and their combination accounts for a 76% yield.

NOTE: *N*-*t*-Butylphthalimide can react with hydrazine hydrate and upon acidification of the reaction mixture *t*-butylamine is obtained in 89–94% yield [30–31].

### 2-3. *Preparation of α-Ethylglutarimide* [32a]



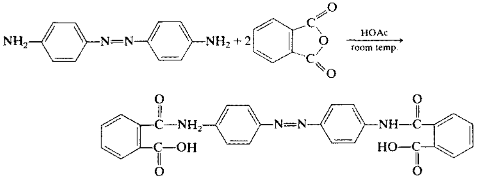
(5)

To a flask equipped with a mechanical stirrer, condenser, and gas inlet tube is added 20.0 gm (0.14 mole) of $\alpha$-ethylglutaric anhydride. The contents are heated to 130–140°C and ammonia gas is rapidly bubbled into the mixture for $\frac{1}{2}$ hr. The mixture is heated slowly over a $\frac{1}{2}$ hr period to 250°C and then distilled to afford 16.9 gm (85%), b.p. 265–280°C, m.p. 107–108°C (from acetone–ether).

Evidently, if reaction temperatures, in an appropriate solvent, are sufficiently high, anhydrides react with amines to form imides. This may even hold true for the formation of *N*-alkylated imides. For example, in 7 ml of glacial acetic acid, 12.7 mmol of 3-*tert*-butylphthalic anhydride and 66.7 mmol of *tert*-butylamine, heated under nitrogen at reflux, gave a 64% yield of *N*,3-di-*tert*-butylphthalimide (m.p. 70°C). The product was isolated from the reaction system by dilution with an ice-water mixture and extraction of the product with methylene dichloride. After removal of the solvent, the product was recrystallized from methanol [32b].

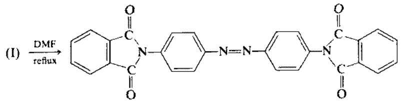
Under milder reaction conditions, the intermediate amide-acid (often referred to as "amic" acids) may be formed. Preparation 2-4 is an example of the conditions for the formation of an amic acid and the imide derived therefrom.

### 2-4. ***Preparation of* N,N′-*Diphthaloyl*-p,p′-*diaminoazobenzene and Its Imidization*** **[32c]**



(6)

(I)



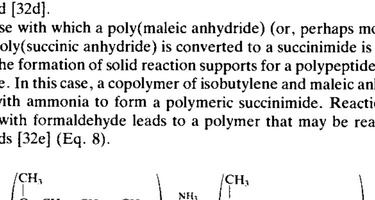
(7)

(*a*) A solution of 0.5 g, (2.36 mmol,) of *p,p′*-diaminoazobenzene and 1.05 g (7.08 mmol) of phthalic anhydride in 9 ml of glacial acetic acid is stirred at room temperature for 1 hr. The reaction mixture is then poured into 25 ml of distilled water. The yellow product is filtered off and recrystallized from ethanol. The yield of the diamic acid (I) is 0.89 g (74%); m.p. 210–212°C; IR (KBr): 3100 (OH), 1665 (C═O), 3278 (NH), 1595 (C═O) and 1541 $\mathrm{cm}^{-1}$ (NH).

(*b*) A solution of 0.50 g (0.98 mmol) of the purified diamic acid (I), prepared in (a) is dissolved in 20 ml of DMF and heated at reflux for 2 hr. The reaction mixture is cooled to room temperature. The golden brown precipitate is filtered off and recrystallized from DMF. The yield of the diimide is 0.37 g (80%), m.p. 360–362°C: IR (KBr)—no amide absorptions, but imide absorptions at 1720 and 1770 $\mathrm{cm}^{-1}$.

Maleic anhydride evidently reacts exothermically with diamines such as ethylenediamine. The reaction mixture has to be cooled with an icebath to maintain a reaction temperature of 20°C in acetone. The amic acid, *N,N'*-dimaleoylethylenediamine is formed in 89.7% yield. Upon refluxing this product in acetic anhydride, the corresponding bis(maleimide) is formed in 62% yield [32d].

The ease with which a poly(maleic anhydride) (or, perhaps more accurately, a poly(succinic anhydride) is converted to a succinimide is of importance in the formation of solid reaction supports for a polypeptide synthesis procedure. In this case, a copolymer of isobutylene and maleic anhydride is treated with ammonia to form a polymeric succinimide. Reaction of this polymer with formaldehyde leads to a polymer that may be reacted with aminoacids [32e] (Eq. 8).



(8)

The reactions of anhydrides to form imides are not confined to their action on ammonia or amines. Hydrazine hydrates may be used to synthesize *N*,*N*′-bis(phthalimide). In a French patent application, a dispersion of *1114* g of tetrabromophthalic anhydride in 1600 g of water heated to 60°C is treated with 60 g of hydrazine hydrate over a 30-min period. Then the temperature is raised to 100°C and held there for 7 hr. The reaction mixture is diluted with another 1600 g of water and heated for another 7 hr at 100°C. From this mixture, a white product is isolated, which contains 40% of *N*,*N*′-bis(tetrabromophthalimide), 30.5% of *N*-amino-tetrabromophthalimide, and 29.5% unreacted tetrabromophthalic anhydride. The product is used in the preparation of flameproofing agents [32f].

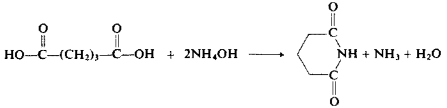
Urea, as has been mentioned previously, may be used to form imides from anhydrides. Recent examples are [32b] and [32g].

Tetracarboxylic anhydrides such as pyromellitic dianhydride and 1,4,5,8-naphthalenetetracarboxylic anhydride react with amides (e.g. formamide) to form the corresponding cyclic mono- and/or diimides. In the case of the reaction with formamide, the process involves the intermediate formation of *N*-formylphthalamic acid [32h].

## B. Reaction of Carboxylic Acids with Ammonia or Amines

Ammonia, ammonia derivatives, or amines react with di- and polycarboxylic acids to give salts which upon heating at 180–300°C afford imides in good yield.

### *2-5. Preparation of Glutarimide* [33]



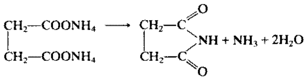
(9)

To a flask containing 70 gm (0.53 mole) of glutaric acid is added 150 ml (2.2 mole) of 28% aqueous ammonia. The mixture is set for distillation and heated for 7 hr as the temperature of the mixture rises from 90° to 180°C. The temperature is held at 170–180°C for $1\frac{1}{2}$ hr or until the evolution of ammonia ceases. The reaction mixture solidifies on cooling and the product is recrystallized from acetone to afford 37.4 gm (63%), m.p. 145–146°C.

It may be advantageous to preform the ammonium salt of dicarboxylic acids prior to the application of enough heat to form the imide. The preparation of succinimide is a case in point.

### 2-6. *Preparation of Succinimide*

$$HOOCCH_2CH_2COOH + 2NH_4OH \longrightarrow$$



(10)

To a flask equipped with a dropping funnel, mechanical stirrer, and a 40 cm long side arm of not less than 10 mm inside diameter is added 236 gm (2.0 mole) of succinic acid. The flask is cooled and 270 ml (4.0 moles) of 28% aqueous ammonia is slowly added with stirring. The flask is rapidly heated with an oil bath until 200 ml of water distils. The temperature of the bath is rapidly raised to 275°C. Succinimide starts to distil over the range 275–289°C, to afford 168 gm of crude product which solidifies on cooling. The intermediate fraction, boiling between 102° and 275°C, is redistilled to afford 10.0 gm of crude succinimide, b.p. 275–289°C. The combined product (178 gm) is added to 178 gm of hot ethanol. The solution is cooled, the crystals filtered, washed with 25 ml of cold ethanol, and dried to afford 163–164 gm (82–83%), m.p. 123–125°C. Approximately 4–5 gm of additional product may be obtained by concentrating the mother liquor.

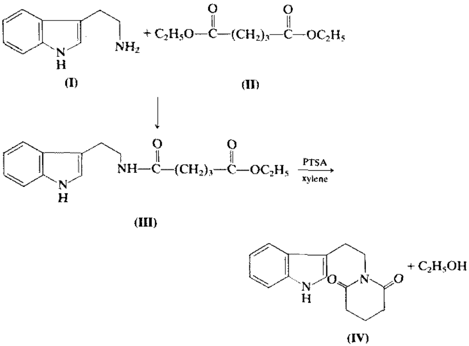
Recent Japanese patents suggested inert aprotic solvents such as cyclic amides (e.g., *N*-methylpyrrolidone, *N*-acetyl-2-pyrrolidone, DMF, or tetramethylurea) and azeotroping solvents (e.g., toluene, *o*-xylene, hexane, or pentane) or other high-boiling solvents (e.g., chlorobenzene or chlorotoluene) as dehydrating agents for the formation of imides from dibasic acids (e.g., 3- and/or 4) hydroxyphthalic acid with a large variety of diamines including diaminosiloxanes such as bis (3-aminopropyl)-tetramethylsiloxane [34b].

## C. Conversion of Ester Amides to Imides

The reaction of primary amines with diesters affords at first the monoester amide, which can subsequently be cyclized to the imide by reaction with *p*-toluenesulfonic acid. The cyclization reaction is carried out in a hydrocarbon solvent using a distillation head to collect the ethanol which forms. This has the advantage of requiring lower temperatures than other methods.

It has been reported that the reaction of aniline with acetylenedicarboxylate esters affords $\alpha$-anilinomaleimides [35a].

### *2-7 Preparation of* N-*(2-Indol-3-ylethyl)glutarimide* [35b]



(11)

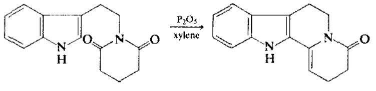
(*a*) *Preparation of ethyl* N-*(2-indol-3-ylethyl)glutaramate (III).* To a flask containing 20.0 gm (0.125 mole) of tryptamine is added 26.0 gm (0.139 mole) of diethyl glutarate. The mixture is heated at 175°C for 18 hr. After this time, $2\frac{1}{2}$ l of chloroform is added. The mixture is refluxed for $\frac{1}{2}$–1 hr, cooled, and filtered. The filtrate is concentrated under reduced pressure to afford a residue, which is crystallized from benzene. The solid product is filtered and recrystallized from methylene chloride–petroleum ether (b.p. 30–60°C) to afford 32.8 gm (47%) of (III), m.p. 101–102°C.

(*b*) *Preparation of* N-*(2-indol-3-ylethyl)glutarimide (IV).* To a flask equipped with a Dean–Stark tube, condenser, and mechanical stirrer is added 31.7 gm (0.105 mole) of ethyl *N*-(2-indol-3-ylethyl)glutaramate, 9.6 gm (0.056 mole) of *p*-toluenesulfonic acid, and 1200 ml of xylene. The mixture is heated for approximately 9 hr under a distillation head until no more ethanol can be removed.* The reaction mixture is filtered, diluted with 1800 ml of petroleum ether, cooled, and filtered to afford 15.0 gm (53%), m.p. 173–175°C (recrystallized from methanol).

---

* Reference 35b states that water forms in this step. This is probably a typographical error. We have modified Eq. 11 and the procedure to reflect the fact that ethanol is formed during this reaction.

NOTE: The product (IV) can be cyclized with phosphorus pentoxide in xylene to afford a 31% yield of 2,3,4,6,7,12-hexahydroindolo[2,3-*a*]-quinolizin-4-one.



IV

(12)

## D. Condensation Reactions of Imide Salts to Give *N*-Alkyl Imides

Lithium, sodium, and potassium imides react with alkyl halide to give *N*-substituted imides in good yield (Eq. 13) [36]. The Gabriel condensation involves a similar reaction. The *N*-alkyl imides are then reacted with aqueous hydrazine solution to give amines [37].

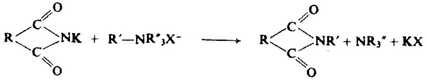
$$>N{-}K + RX \longrightarrow >N{-}R + KX \qquad (13)$$

Potassium naphthalimide [38] has been suggested as a reagent for the identification of alkyl halides [39]. The reaction is carried out in dimethylformamide and is successful for converting primary halides to *N*-alkylnaphthalimides, but the yields are low with secondary halides. Tertiary halides do not react. The product imides are white crystalline solids which can be recrystallized from various alcohols or their alcohol–water mixtures. Several examples are shown in Table IV.

Two moles of potassium phthalimide react under anhydrous conditions with 1 mole of diiodomethane to give *N,N'*-methylenediphthalimide [40]. Succinimide reacts with ethylene dibromide or trimethylene bromide in the presence of sodium ethoxide to give *N*-bromoalkyl derivatives [41]. (See Table V for other reactions of this type.)

Silver derivatives of imides react with alkyl halides to give N-alkylated products [42a,b].

Potassium phthalimide reacts with quaternary ammonium salts to eliminate the volatile tertiary amine and give the N-alkylated product [43].



$$R(CO)_2NK + R'{-}NR''_3X^- \longrightarrow R(CO)_2NR' + NR_3'' + KX \qquad (14)$$

TABLE IV

*N*-ALKYLNAPHTHALIMIDES[a]

| *N*-Alkyl substituent | Yield[b] (%) | M.p. (°C) | Solvent[c] |
|---|---|---|---|
| Methyl | 92 | 206.5[d] | A |
| Ethyl | 98 | 154[e] | A |
| Propyl | 90 | 158–159 | B |
| Isopropyl | 12 | 163–164 | C |
| Butyl | 95 | 96.5–97 | B |
| *sec*-Butyl | 4 | 111–112 | C |
| Amyl | 55 | 86 | C |
| Isoamyl | 57 | 104–105 | C |
| 1-Methylbutyl | 4 | 69 | D |
| Hexyl | 75 | 81.5–82.5 | B |
| Heptyl | 90 | 70.5–71.5 | C |
| Octyl | 43 | 42.5–43.5 | A |
| Nonyl | 95 | 56.5–57 | C |
| Decyl | 95 | 52 | A |
| Undecyl | 80 | 53–53.5 | C |
| Dodecyl | 95 | 56–57 | E |
| Benzyl | 82 | 95–96 | B |

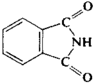
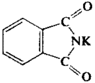
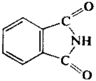
[a] All melting points are corrected. [b] Crude yield based on potassium naphthalimide. [c] Recrystallizing solvent: A = 95% ethanol; B = isopropanol; C = isopropanol–water; D = methanol–water; E = methanol. [d] G. F. Jaubert, *Chem. Ber.* **28**, 360 (1895) reported m.p. 205°C. [e] G. F. Jaubert, *Chem. Ber.* **28**, 360 (1895), reported m.p. 148°C. [Reprinted from M. A. Devereaux and H. B. Donahoe, *J. Org. Chem.* **25**, 457 (1960). Copyright 1960 by the American Chemical Society. Reprinted by permission of the copyright owner.]

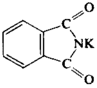
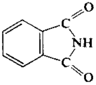
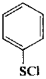
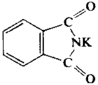
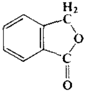
### *2-8. General Procedure for the Preparation of* N-*Alkylnaphthalimide* [39]

To a flask equipped with reflux condenser and containing 2.35 gm (0.01 mole) of potassium naphthalimide is added 0.01 mole of the appropriate alkyl halide in 15 ml of dimethylformamide. The mixture is refluxed for 1 hr, cooled, the potassium bromide removed by filtration, and then cold water is added to the filtrate to precipitate the product imide. The *N*-alkylnaphthalimide is filtered, dissolved in ether, filtered, and the ether is removed from the filtrate under reduced pressure to afford the crude product. Several examples using this procedure are described in Table V.

TABLE V

PREPARATION OF *N*-ALKYLPHTHALIMIDES

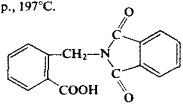
| Imide (moles) | Base (moles) | Solvent (ml) | R—X (moles) | Reaction conditions | | Yield (%) | M.p. (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|
| | | | | Temp. (°C) | Time (hr) | | | |
| <br>(2.5) | $K_2CO_3$<br>(2.5) | DMF<br>(1.667) | $(ClCH_2CH_2)_2$<br>(1.0) | 150 | 12 | 88 | — | *d* |
| <br>(0.84) | — | — | $BrCH_2CH_2Br$<br>(2.4) | 180–190 | 12 | 69–79 | 78–80[a] | *e* |
| <br>(2.04) | (1.09) | — | $C_6H_5CH_2Cl$<br>(2.37) | 179 | 3 | 74–77 | 116<br>(from $CH_3COOH$) | *f* |
| (2.04) | (1.09) | — | $Br(CH_2)_3Br$<br>(4.95) | 167 | 2 | 40–44 | 72[b] | *f* |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| <br>(0.135) | — | — | $C_6H_5CH_2CH_2Br$<br>(0.108) | 180–200 | 2–3 | — | 131–132 | *f* |
|  | $(C_2H_5)_3N$<br>(0.5) | (200) | <br>(0.50) | 0–25 | 1½ | 95 | 160–161 | *g* |
| <br>(0.81) | — | (500) |  | 150 | 5 | 60–67 | 265–266.5[c] | *h* |

---

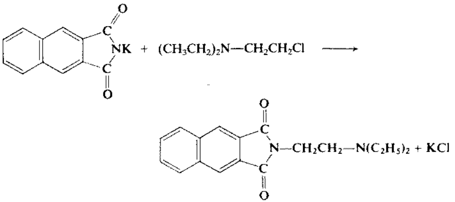
[a] Approx. 10 gm of crude diphthalimidoethane is obtained.

[b] The residue, insoluble in petroleum ether, affords after one recrystallization from acetic acid 100–120 gm of pure α,α-diphthalimidopropane, m.p., 197°C.

[c] 

[d] B. Vassel, U.S. Pat. 2,757,198 (1956). [e] P. L. Salzberg and J. V. Supniewski, *Org. Syn. Coll.* **1**, 119 (1941). [f] H. R. Ing and R. H. F. Manske, *J. Chem. Soc.* 2348 (1926). [g] M. Behforouz and J. E. Kerwood, *J. Org. Chem.* **34**, 51 (1969). [h] J. Bornstein, P. E. Drummond, and S. F. Bedell, *Org. Syn. Coll.* **3**, 810 (1963).

### *2-9. Preparation of N-(2-Diethylaminoethyl)naphthalimide* [44]

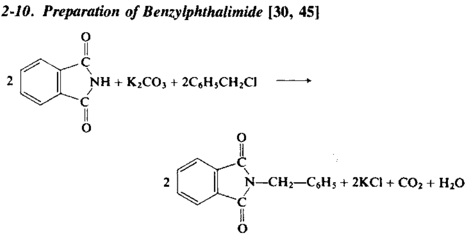


(15)

To a flask containing a hot solution of 30.0 gm (0.152 mole) of naphthalimide in 100 ml of ethanol is added all at once a solution of 9.94 gm (0.152 mole) of 85% potassium hydroxide in 200 ml of ethanol. The mixture is heated gently while stirring until all the potassium naphthalimide precipitates. At this point 37 gm (0.26 mole) of diethylaminoethyl chloride is added and the mixture is refluxed for about $\frac{1}{2}$ hr, or until the grayish potassium naphthalimide salt goes into solution with the formation of an orange color. The reaction mixture is cooled to room temperature, the potassium chloride is filtered, the alcohol removed, and the residue finally heated to 100°C at 1 mm Hg pressure for a short time. The resulting solid is redissolved in ethanol and treated with a stream of dry hydrogen chloride gas or with excess alcoholic hydrogen chloride. On cooling, the product precipitates as the hydrochloride, which is filtered and dried to afford 40.0 gm (90%), m.p. 155–156°C (dec.)

NOTE: A similar procedure is used to obtain a 65% yield of *N*-(2-dimethylaminoethyl)naphthalimide hydrochloride, m.p. 251°C (dec.) and 64% yield of *N*-(2-morpholinoethyl)naphthalimide hydrochloride, m.p. 244°C (dec.).

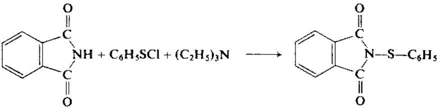
### *2-10. Preparation of Benzylphthalimide* [30, 45]



(16)

In a flask equipped with a reflux condenser, a mixture of 300 gm (2.04 mole) of phthalimide, 140 gm (1.09 mole) of potassium carbonate, and 300 gm (2.37 mole) of benzyl chloride is refluxed for 3 hr. The excess benzyl chloride is removed by steam distillation and the benzyl phthalimide which crystallizes out is filtered by suction. The product is washed with water, with 400 ml of 60% ethanol, and then dried to afford 360–375 gm (74–77%), m.p. 116°C (recrystallized from acetic acid).

### *2-11. Preparation of* N-*(Phenylthio)phthalimide* [46a]



(17)

(*a*) *Preparation of benzenesulfenyl chloride.* To a stirred solution of 55 gm (0.5 mole) of benzenethiol in 300 ml of *n*-pentane at 0°C is added chlorine gas until an assay (GC) of the resulting red-orange solution shows quantitative conversion to the sulfenyl chloride. The reaction usually requires about 39 gm (0.6 mole) of chlorine.

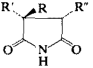
(*b*) *Reaction of benzenesulfenyl chloride with phthalimide.* To a stirred solution of 73.5 gm (0.5 mole) of phthalimide in 200 ml of dimethylformamide is first added 60 gm (0.6 mole) of triethylamine. Then the sulfenyl chloride solution from (*a*) is slowly added dropwise. The reaction mixture is stirred for $\frac{1}{2}$ hr, poured into 2 liters of cold water, filtered, and dried to afford 121 gm (95%), m.p. 160–161°C (recrystallized from ethanol).

Complex imides such as camphorimide and 9,10-dihydroanthracene-9,10-endo-$\alpha,\beta$-succinimide have been alkylated in methylene dichloride with alkyl halides, using tetrabutylammonium bromide as a phase-transfer catalyst and aqueous potassium hydroxide as a base [46b].

*N*-Bromophthalimide is readily prepared by treating an aqueous slurry of phthalimide at 0°C with bromine. (**CAUTION**): This product, m.p. 198–202°C [46c], has been used as a source of phthalimidyl radicals. Dimethylglutarimidyl, succinimidyl, and 1,8-naphthalenedicarboximidyl radicals have been prepared by appropriately modified variations of this procedure [46c, 46d]. These free radicals may add to electron-rich alkenes to yield *N*-bromoalkylphthalimides. The imidyl-free radicals are generated in Pyrex pressure tubes with a 400-W, medium-pressure mercury arc lamp [46c, 46d]. The techniques used in this procedure may require more development to be suitable for the general preparative laboratory.

Imides have also been *N*-alkylated with *O*-alkylidicyclohexylisoureas in DMF solution under neutral conditions [46e].

Certain aziridine complexes of molybdenum hexacarbonyl, when reacted with sodium diethyl malonate, in tetrahydrofuran, at −78°C, led to stereospecific imides of structure (V)

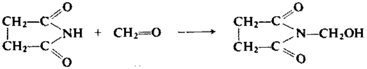


(V)

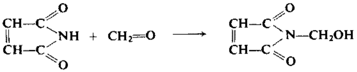
where R and R′ came from the aziridine starting material and R″ from a C-alkylated diethyl malonate [46f].

## E. Reaction of Imides with Aldehydes and Ketones

Without pH adjustment, formaldehyde (40%) reacts rapidly with phthalimide to afford *N*-hydroxymethylphthalimide (Eq. 19) [47a,b]. Succinimide requires potassium carbonate in boiling formaldehyde to give *N*-hydroxymethylsuccinimide (Eq. 18) [48]. Maleimide requires a trace of potassium carbonate to react with formaldehyde to afford *N*-hydroxymethylmaleimide (Eq. 19) [49].

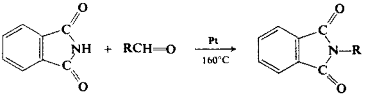


(18)



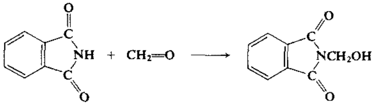
(19)

Phthalimide reacts with acetone under pressure in the presence of 0.04% platinum supported on alumina and heating to 160°C, to give the *N*-isopropyl derivative. Phthalimide reacts with isobutyraldehyde under similar conditions to afford *N*-isobutylsuccinimide (Eq. 20) [50a]. The condensation reactions of phthalimide are described in the Miscellaneous Methods Section.



(20)

### 2-12. *Preparation of* N-*Hydroxymethylphthalimide* [47a]


(21)

To a flask equipped with a mechanical stirrer and condenser is added 511 gm (3.47 moles) of phthalimide, 260 ml of 40% formalin (3.47 moles), and 1750 ml of water. The mixture is refluxed for about 5–10 min or until a clear solution results (if any insoluble material remains, it is first filtered). Then the mixture is cooled for several hours. The resulting product is filtered with suction, washed with cold water, and air-dried to afford 594 gm (96%), m.p. 137–141°C.

NOTE: The product should not be oven-dried since it decomposes with the loss of formaldehyde. Recrystallization of the product from ethanol affords 94% recovery of the original material with the same melting point range.

## 3. FORMATION OF POLYIMIDES

(See also Section 2A and Table III.)

The reaction of copolymers of isobutylene and maleic anhydrides with ammonia to form polymeric imides has been discussed in Eq. 8. These materials are of interest in biotechnology. For example, after reaction with formaldehyde, the *N*-hydroxymethylsuccinimide grouping may be esterified with the carboxylic acid end of an amino acid. The resulting product has free amino groups, which can then undergo further reactions with amino acids to form protein analogs [32e].

In the present discussion, we term such derivatives of maleic anhydrides, "polymeric imides." *Polyimides*, on the other hand, are condensation polymers, in which the polymeric backbone consists of imide moieties. Typically such polyimides are formed by reaction of dianhydrides (e.g., pyromellitic anhydride or benzophenone tetracarboxylic dianhydride) with diamines or polyamines. The reaction usually proceeds via the intermediate formation or "amic" acids, which are then cyclized to form polyimides. The products are of interest as high-performance resins.

A detailed discussion of polyimide chemistry is beyond the scope of this chapter. Reviews that are of interest are [3d], [26b], and [50b]. Some recent polyimide preparations are

(1) Aliphatic bis(nadimides) have been synthesized from nadic anhydride and diamines [50c].

(2) Polyimides were formed by reacting maleic anhydride with a polyamine formed by condensing 1,3-benzenedialdehyde with aniline [50d].

(3) Preparation of *N*-(1,3-dithiol-2-yl)imides by an insertion reaction of 1,3-dithiolium carbenes [50e].

(4) Preparation of unsaturated polyimide monomers by addition of 4,4′-diaminodiphenylmethane in acetone/DMF to an acetone solution of maleic anhydride [50f].

(5) Polymerization by cycloaddition of 3-phenylsydnone with a bis(maleimide) [50g].

(6) Formation of polyimides from substituted phthalic anhydrides such as trimellitic anhydride acid chloride with diamines [50h].

(7) Preparation of flame-retardant compositions from tetrachlorophthalic anhydride and tribromoaniline [50i].

(8) Preparation of a precondensate of pyromellitic dianhydride with benzidine in DMF, followed by dehydration in acetic anhydride [50k].

NOTE: Benzidine is no longer available in the U.S. because of high carcinogenicity.

(9) Formation of poly(*o*-amino-*o*-carboxy)amides from polyaminoaromatic compounds with pyromellitic dianhydride in DMF. The resulting amides were converted to imides by heating with pyridine-acetic anhydride [50l].

(10) Synthesis of melt-processible polyimides from 4,4′-bis(3,4-dicarboxyphenoxy)diphenylsulfide dianhydride in bis(2-methoxyethyl) ether [50m].

(11) Preparation of tin-containing polyimides, based on 3,3′,4,4′-benzophenone tetracarboxylic dianhydride or on pyromellitic dianhydride with 4,4′-oxybis (aniline) [50n].

(12) Synthesis and properties of Star and linear imide oligomers with reactive end groups [50o].

(13) Imide oligomers with internal acetylene groups in the backbone and biphenylene end groups [50p].

(14) The synthesis, curing, and thermal properties of imide oligomers containing reactive acetylenic and bis(phenylene) groups, as well as perfluroisopropylidene connecting groups [50q].

(15) Synthesis of polyimides in which the diamine starting material was 1,2-bis(*p*-aminophenoxy)propane [50r].

(16) Polyimides derived from nitrogen-linked diamines such as *N*,*N*′-bis(4-aminophenyl)-*N*,*N*′-dimethylethylene-diamine [50s].

(17) Polyimides derived from two aminonaphthalene moieties linked by polyethylene oxide units [50t].

(18) Synthesis of imide-arylene ether phenylquinoxaline random copolymers [50u].

(19) Synthesis of poly(amic dialkylamides) from poly(isoimides) derived from pyromellitic dianhydride and tetramethylbenzidine with secondary amines [50v].

(20) Segmented copolymer blends of polybenzidiazole/polyimide and polybenzimidazole/poly(siloxane imide) [50x].

## 4. MISCELLANEOUS METHODS

(1) Reaction of diesters with ammonia, ammonia derivatives, or amines [51a,b].

(2) Reaction of acid halides with ammonium halides under anhydrous conditions [52].

(3) The thermal conversion of diamides or the monoammonium monoamide salts to imides [53a–c].

(4) Thermal (250°C) rearrangement of acenaphthenequinone monoxime to give 1,8-napthalimide [54].

(5) Thermal conversion of monoamides of dicarboxylic acids to imides [55].

(6) Hydrolysis of dinitriles to the half-nitrile half-amide and subsequent hydrolysis to the imide [56].

(7) Oxidation of $\alpha$-nitronaphthalene with air or oxidation of a mixture of xylene with air and ammonia using $V_2O_5$ catalyst to give phthalimide [57].

(8) Oxidation of pyrrole with hydrogen peroxide to succinimide [58].

(9) Oxidation of pyrrole over aluminum powder and air to succinimide [59].

(10) Oxidation of piperidine over aluminum power and air to glutarimide [60].

(11) Chromic acid oxidation of pyrrole to maleimide [61].

(12) Electrolytic oxidation of pyrrolidone carboxylic acid in dilute sulfuric acid with lead oxide, platinum, or carbon electrodes to give succinimide [62].

(13) Oxidation of 1-nitronaphthalene to phthalimide [63].

(14) Oxidation of 2-formylpyrrole by hydrogen peroxide to succinimide, [64].

(15) The vapor-phase catalytic reaction of isoquinoline to afford phthalimide and some pyridine [65].

(16) Vapor-phase reaction of alkanes with ammonia and oxygen in the presence of metallic catalysts to afford imides [66].

(17) Reaction of unsaturated aliphatic amides with carbon monoxide under pressure in the presence of metallic salts or cobalt carbonyl to afford imides in 65–96% yields [67].

(18) Reaction of methanolic succinonitrile with liquid ammonia and hydrolysis of 2,5-diimopyrrolidone to give succinimide [68].

(19) Preparation of glutarimide by the distillation of a mixture of powdered anhydrous sodium cyanide and γ-butyrolactone at 200°C [69].

(20) Reaction of the hydrochloride of 5-cyano-l-hydroxypentylidenimine at 180°C to afford 25% adipimide [70].

(21) Reaction of cyanovaleric acid at 230°C to afford adipimide [71].

(22) The reaction of sulfur monochloride with phthalamide or succinamide in dioxane to afford the corresponding imides [72].

(23) Reaction of sulfur monochloride in dioxane with glutaric acid diamide [73].

(24) Reaction of sulfur monochloride in dioxane with succinic acid diamide to afford succinimide and ammonia [74].

(25) Condensation of chloroacetamide with ethyl sodioacetoacetate to give acetylsuccinimide [75].

(26) Reaction of *N*-amino-1,8-napthalamide with sodium nitrate and acetic acid or with sodium hypobromite in alkali to give 1,8-naphthalimide [76].

(27) Reaction of succinonitrile with hydroxylamine in warm aqueous alcohol to give 5-hydroxyimino-2-pyrrolidone, which is subsequently reacted with sodium nitrite in aqueous acid to give succinimide [68].

(28) Reaction of bis(2-chloroethyl) ether with sodium cyanide to afford succinimide [73].

Note: Bis(2-chloroethyl)-ether is an extremely hazardous cancer-causing agent.)

(29) Beckmann rearrangement of acetonaphthane quinone monoxime using acetic acid, hydrogen chloride in acetic anhydride, sulfonyl chloride in dry pyridine, or 70% sulfuric acid [77].

(30) The Beckmann rearrangement of 1,2-cyclohexanedioxime in liquid sulfur dioxide afford 1-azo-7-oximocycloheptan-2-one which is then subsequently cyclized by means of thionyl chloride to adipimide [78].

(31) Reaction of cyclohexanecarbonyl chloride with phenyl isocyanate in benzene solution at 25°C in the presence of triethylamine to afford imides [79].

(32) Reaction of diphenylketene with phenyl isocyanate to afford *N*-phenyldiphenylmalonimide at 220°C [80].

(33) The reaction of ethyl phthalate with magnesium aminoiodide in ether and subsequent reaction with water affords phthalimide [81].

(34) Reaction of isatoic anhydride with ammonia to afford phthalimide [82].

(35) The reaction of 1,2-dibromonaphthalene with copper cyanide and pyridine in a sealed tube at 200°C and then subsequent treatment of the mixture with dilute hydrochloric acid to afford 1,2-naphthalimide [83].

(36) Preparation of 2,2′-diphenyldicarboximide by heating in a sealed tube at 225–240°C a mixture of 2,2′-diphenyldicarboxylic acid and acetonitrile [84].

(37) Preparation of 2,2′-diphenyldicarboximide by heating to 130°–140°C 9,10-phenanthraquinone monoxime with HCl gas in a mixture of acetic acid and acetic anhydride all enclosed in a sealed tube [84].

(38) Preparation of *N*-methylphthalimide by the reaction of 40% formaldehyde solution at 150–160°C with phthalimide [85].

(39) Succinimide reacts with 40% formaldehyde at 150–160°C to afford *N*,*N*-methylenedisuccinimide [85].

(40) Preparation of *N*,*N*-methylenediphthalimide by the reaction of phthalimide with hexamethylenetetramine at 130°C [86].

(41) Preparation of *N*-methylimides by the reaction of diazomethane with phthalimide or succinimide [87].

(42) Preparation of *N*-vinylphthalimide by the reaction of acetylene at elevated temperatures and pressures with phthalimide using small amounts of cadmium acetate as a catalyst [88].

(43) Reaction of phthalimide with propylene oxide at 170°C to give a low yield of *N*-propoxyphthalimide and a large amount of the unexpected product, *N*-(2-hydroxyethyl)phthalimide [89].

(44) Preparation of *N*-hydroxymethylsuccinimide by the reaction of succinimide with boiling formaldehyde and potassium carbonate [48].

(45) Preparation of *N*-arylaminomethylsuccinimide by the reaction of a primary arylamine with succinimide and formaldehyde. Aliphatic amines afford bis(succinimide) alkylamine [90].

(46) Preparation of *N*-hydroxyethylimides by the reaction of imides with ethylene carbonate at 190°C in the presence of 0.5% sodium carbonate [91].

(47) Acetylation of imides with acetic anhydride [38].

(48) Acetylation of imides by reaction with ketenes using a sodium acetate catalyst [92].

(49) Preparation of stearylated imides by heating imides with isopropenyl stearate and an acid catalyst [93].

(50) Preparation of *N*-aminoimides [94].

(51) Preparation of *N*-haloimides by reaction of HOCl and HOBr with imides (succinimide or phthalimide) [95].

(52) Reactions of halogens with imides to give *N*-haloimides [96a–c].

(53) Nitration of aromatic imides or *N*-aryl imides [97a–c].

(54) Reaction of methyl vinyl ketone with phthalimide to give l-phthalimido-3-butanone [98].

(55) Reaction of succinimide with phenyl isocyanate to give l-succinyl-3-phenylurea. Phthalimide reacts with phenyl isocyanate to give *N*-phenylphthalimide with elimination of hydrocyanic acid [99].

(56) Reaction of sodium succinimide with β-propiolactone to afford 3-succinimidopropionic acid [100].

(57) Reduction of aromatic imides to give cyclohexyldicarboximides [101a,b].

(58) Reduction of maleimide to succinimide [102a,b].

(59) Complexes of maleimide with hydroquinone [103].

(60) Preparation of nitromethylphthalimide and *N*-nitromethylsuccinimide by the reaction of the corresponding *N*-bromomethylimides with silver nitrite [104].

(61) Hydrolysis of monothiosuccinimides to imides [105].

(62) Preparation of naphthalimide by the reaction of sodium azide and 1,8-naphthalenedicarboxylic acid in DMF at 154°C [106].

(63) Reaction of dimethylsulfoxonium methylide with *N*-methyl-2-arylmaleimides to afford 1-aryl-1,2-cyclopropanedicarboximides [107].

(64) Preparation of succinimide by the reaction of succinonitrile with ammonia and subsequent hydrolysis of the intermediate product (succinimidine) [108].

(65) Preparation of α,α′-dicyano-β-ethyl-β-methylglutarimide by the reaction of ethyl cyanoacetate with ethyl acetate, ammonia, and ammonium acetate in ethanol as a solvent [109].

(66) Preparation of β-methyl-β-phenyl-α,α′-dicyanoglutarimide by the reaction of cyanoacetamide with ethyl(l-phenylethylidene)cyanoacetate in the presence of ethanolic sodium ethoxide [110].

(67) Reaction of imides with vinyl esters [111].

(68) Thermal conversion of glutaric acid monoamide to glutarimide [112].

(69) Cyclization of *N*-succinylglycine dimethyl ester to 2,5-diketo-l-pyrrolidineacetic acid methyl ester [113].

(70) Preparation of succinimide from succinic acid monomethyl ester monoamide [114].

(71) Preparation of acyclic imides [115].

(72) Reaction of acid halides with ammonium halides under anhydrous conditions to give imides [116].

(73) Polymerization of ethylene with *N*-vinylimides [117].

(74) Reaction of glutarimide, 3,5-morpholinedione, and 3,5-thiomorpholinedione with 2 molecular equivalents of sodium amide in liquid ammonia and subsequent reaction with alkyl halides and carbonyl compounds affords α-substituted derivatives [118].

(75) Oxidation of lactams with hydroperoxide or peroxyacids in the presence of Mn(II) or (III) salts at 0°C [119].

(76) The synthesis of macrocyclic imides by the peracid oxidation of enelactams [120].

(77) Reaction of 3-carboxyacryloylhydrazines and the preparation of maleimides, isomaleimides, and pyridazinones [121].

(78) Formation of imides by reaction of aminotriphenylpyridinium tetrafluoroborate with active chlorides and heterocumulenes [122].

(79) A review on recent developments in carbodiimide chemistry [123].

(80) Synthesis of β-keto imides [124].

(81) Reaction of aliphatic imides with oxalyl chloride [125].

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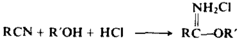
## 1. INTRODUCTION

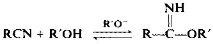
Imidate (imino ethers or imido esters) hydrochlorides were first reported in 1877 by Pinner [1a,b], who prepared them by the reaction of the appropriate alcohol and nitrile in the presence of anhydrous hydrogen chloride (Eq. 1).



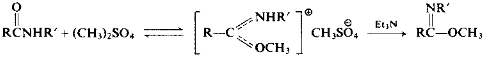
$$RCN + R'OH + HCl \longrightarrow RC(=NH_2Cl){-}OR' \qquad (1)$$

The free imidate is obtained by treatment of the salt with an aqueous potassium carbonate solution and is immediately extracted with ether.

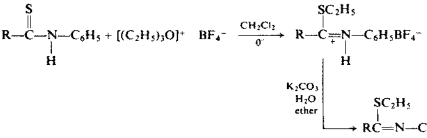
Some other important methods of preparing imidates are summarized in Eqs. 2–9.



$$\mathrm{RCN + R'OH \overset{R'O^-}{\rightleftharpoons} R{-}\overset{NH}{\overset{\|}{C}}{-}OR'} \tag{2}$$

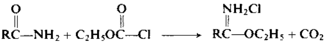


$$\mathrm{R\overset{O}{\overset{\|}{C}}NHR' + (CH_3)_2SO_4 \rightleftharpoons \left[R{-}C{\overset{\nearrow NHR'}{\underset{\searrow OCH_3}{}}}\right]^{\oplus} CH_3\overset{\ominus}{S}O_4 \xrightarrow{Et_3N} R\overset{NR'}{\overset{\|}{C}}{-}OCH_3} \tag{3}$$

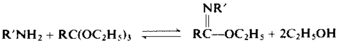


$$\mathrm{R{-}\overset{S}{\overset{\|}{C}}{-}\underset{H}{\underset{|}{N}}{-}C_6H_5 + [(C_2H_5)_3O]^+\ \ BF_4^- \xrightarrow[0^\circ]{CH_2Cl_2} R{-}\overset{SC_2H_5}{\overset{|}{C}}\underset{+}{=}\underset{H}{\underset{|}{N}}{-}C_6H_5BF_4^-} \tag{4}$$

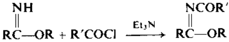
$$\mathrm{\xrightarrow{K_2CO_3,\ H_2O,\ ether} R\overset{SC_2H_5}{\overset{|}{C}}{=}N{-}C_6H_5}$$



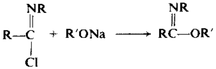
$$\mathrm{R\overset{O}{\overset{\|}{C}}{-}NH_2 + C_2H_5O\overset{O}{\overset{\|}{C}}{-}Cl \longrightarrow R\overset{NH_2Cl}{\overset{\|}{C}}{-}OC_2H_5 + CO_2} \tag{5}$$



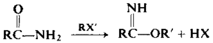
$$\mathrm{R'NH_2 + RC(OC_2H_5)_3 \rightleftharpoons R\overset{NR'}{\overset{\|}{C}}{-}OC_2H_5 + 2C_2H_5OH} \tag{6}$$



$$\mathrm{R\overset{NH}{\overset{\|}{C}}{-}OR + R'COCl \xrightarrow{Et_3N} R\overset{NCOR'}{\overset{\|}{C}}{-}OR} \tag{7}$$

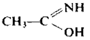


$$\mathrm{R{-}\underset{Cl}{\underset{|}{\overset{NR}{\overset{\|}{C}}}} + R'ONa \longrightarrow R\overset{NR}{\overset{\|}{C}}{-}OR'} \tag{8}$$



$$\mathrm{R\overset{O}{\overset{\|}{C}}{-}NH_2 \xrightarrow{RX'} R\overset{NH}{\overset{\|}{C}}{-}OR' + HX} \tag{9}$$

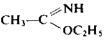
The nomenclature of imidates in the older literature is confusing because these compounds have been described as imino ethers, imido esters, imidic esters, or imidoates, A similar nomenclature exists for the corresponding thio analogs. The *Chemical Abstracts* system of nomenclature, which names this class of compounds after the parent imidic acid and terms them imidates, is used in this chapter. Thus, for example,



$CH_3{-}C(=NH)OH$

Acetimidic acid

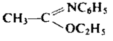
(I)



$CH_3{-}C(=NH)OC_2H_5$

Ethyl acetimidate

(II)

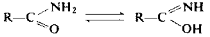


$CH_3{-}C(=NC_6H_5)OC_2H_5$

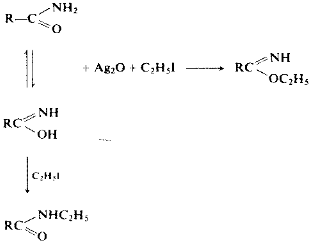
Ethyl *N*-phenylacetimidate

(III)

Free imidic acids (Eq. 10) have not been isolated, but they may be reaction intermediates, as in the silver oxide-catalyzed alkylation of amides (Eq. 11). In the absence of silver oxide, *N*-alkyl amides are obtained.



$$R{-}C(=O)NH_2 \rightleftharpoons R{-}C(=NH)OH \qquad (10)$$

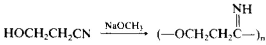


$$R{-}C(=O)NH_2 \rightleftharpoons RC(=NH)OH;\quad + Ag_2O + C_2H_5I \longrightarrow RC(=NH)OC_2H_5 \qquad (11)$$

$$RC(=NH)OH \xrightarrow{C_2H_5I} RC(=O)NHC_2H_5$$

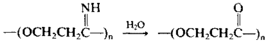
Some of the areas where imidates have found use are in the synthesis of primary [2] and tertiary amines [3], polymers [4], ortho esters [4–7], *s*-triazine systems [8], amidines [9–11], imidazoles [12a,b], 4(5)-imidazolones [13a,b], imidazolines [14], benzimidazoles [15a,b], oxazoles [16], oxazolines [17], benzoxazoles [18], thiazolines [19], dihydroxazines [20,21], and in the preparation of potential chemotherapeutic agents [22a–h]. The syntheses of acyclic [23] and cyclic [24a] imido esters have been reviewed earlier.

The preparation of polymeric imidates has been reported to occur via the reaction of ethylene cyanohydrin [24b].



$$\mathrm{HOCH_2CH_2CN} \xrightarrow{\mathrm{NaOCH_3}} (-\mathrm{OCH_2CH_2}\overset{\overset{\mathrm{NH}}{\|}}{\mathrm{C}}-)_n \tag{12}$$

The exothermic reaction is base catalyzed ($\mathrm{NaOCH_3}$, NaOH, $\mathrm{KOCMe_3}$) and preferably should be carried out in the absence of water. The polymer is purified by quickly dissolving in water and reprecipitating using acetonitrile. Prolonged contact with water leads to polyesters

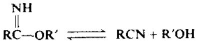


$$-(\mathrm{OCH_2CH_2}\overset{\overset{\mathrm{NH}}{\|}}{\mathrm{C}}-)_n \xrightarrow{\mathrm{H_2O}} -(\mathrm{OCH_2CH_2}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{C}}-)_n \tag{13}$$

Other uses for imidates have recently been reported to be the conversion to (a) guanidines [24c], (b) pyrimidines [24c,d], (c) piperidines [24e], (d) alkoxyoxaziridines (via oxidation of the imidate esters with *m*-chloroperbenzoic acid) [24f], (e) *N*-(*a*-methoxyalkyl)amides [24e], (f) quinazolinones [24h] and (g) esters or thioesters [24i].

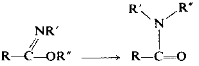
Imidate amines and their stereochemistry have been recently reported [24j].

Most of the aliphatic imidates are usually liquids which can be distilled. The aromatic imidates decompose when heated to yield the corresponding nitrile and alcohol (Eq. 14) [1b]



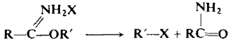
$$\mathrm{R}\overset{\overset{\mathrm{NH}}{\|}}{\mathrm{C}}-\mathrm{OR'} \rightleftharpoons \mathrm{RCN} + \mathrm{R'OH} \tag{14}$$

Liquid N-substituted imidates can be distilled under reduced pressure to give the pure products. However, heating at elevated temperatures causes a rearrangement to N,N-disubstituted amides [25], known as the Chapman rearrangement (Eq. 15) (26).

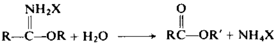


$$\mathrm{R}-\overset{\overset{\mathrm{NR'}}{/\!/}}{\mathrm{C}}-\mathrm{OR''} \longrightarrow \mathrm{R}-\overset{\overset{\mathrm{R'}\diagdown\mathrm{N}\diagup\mathrm{R''}}{|}}{\mathrm{C}}=\mathrm{O} \tag{15}$$

Imidate salts upon heating decompose to the corresponding alkyl halide and amide (Eq. 16) [27]. In water, the imidate salts hydrolyze to the corresponding esters and ammonium salts (Eq. 17) [1b].



$$\mathrm{R}-\overset{\overset{\mathrm{NH_2X}}{/\!/}}{\mathrm{C}}-\mathrm{OR'} \longrightarrow \mathrm{R'}-\mathrm{X} + \mathrm{R}\overset{\overset{\mathrm{NH_2}}{|}}{\mathrm{C}}=\mathrm{O} \tag{16}$$



$$\mathrm{R}-\overset{\overset{\mathrm{NH_2X}}{\|}}{\mathrm{C}}-\mathrm{OR} + \mathrm{H_2O} \longrightarrow \mathrm{R}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{OR'} + \mathrm{NH_4X} \tag{17}$$

## 2. CONDENSATION REACTIONS

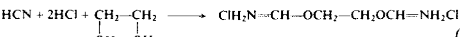
### A. Pinner Reaction

The original Pinner method shown in Eq. (1) is still widely used and consists of condensing a nitrile with an alcohol under anhydrous conditions at 0°C in the presence of hydrogen chloride or bromide [1a,b]. Solvents such as ether [28], dioxane [29], dimethyl cellosolve [30], chloroform [22g], benzene [31] and nitrobenzene [22g] are sometimes employed as diluents and as an aid to crystallization of the imidate salt. The use of excess alcohol may cause ortho ester formation.

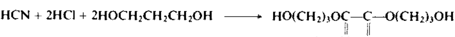
The imidate hydrochlorides are isolated by filtration, washing with anhydrous solvent, and drying under reduced pressure in a vacuum desiccator containing concentrated sulfuric acid or solid sodium hydroxide.

Methanol and ethanol are the most widely used alcohols in the Pinner synthesis, as seen in Table I; however, propyl [32], isopropyl [33], butyl [32], isobutyl [1a], *sec*-butyl [27], octyl [34], decyl [34], and benzyl [35a] alcohols have also given satisfactory results. More-recent examples of the usefulness of the Pinner reaction are worth consulting [35b,c,d,e].

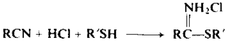
Glycols [36] and diols [30] are also effective in the Pinner synthesis (Eqs. 18, 19), as well as mercaptans (Eq. 20) [37a–c], phenols (Eq. 21) [38a,b], and thiophenols (Eq. 22) [39].



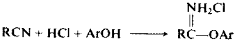
$$HCN + 2HCl + \underset{OH}{\underset{|}{C}H_2}\text{—}\underset{OH}{\underset{|}{C}H_2} \longrightarrow ClH_2N{=}CH\text{—}OCH_2\text{—}CH_2OCH{=}NH_2Cl \qquad (18)$$



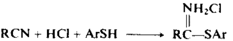
$$HCN + 2HCl + 2HOCH_2CH_2CH_2OH \longrightarrow HO(CH_2)_3O\underset{ClH_2N}{\underset{\|}{C}}\text{—}\underset{NH_2Cl}{\underset{\|}{C}}\text{—}O(CH_2)_3OH \qquad (19)$$



$$RCN + HCl + R'SH \longrightarrow R\overset{NH_2Cl}{\overset{\|}{C}}\text{—}SR' \qquad (20)$$



$$RCN + HCl + ArOH \longrightarrow R\overset{NH_2Cl}{\overset{\|}{C}}\text{—}OAr \qquad (21)$$



$$RCN + HCl + ArSH \longrightarrow R\overset{NH_2Cl}{\overset{\|}{C}}\text{—}SAr \qquad (22)$$

The use of substituted nitriles in the Pinner synthesis leads to certain limitations.

Steinkopf and Malinowski [40] found that α- and β-halogen-substituted nitriles reacted normally in the Pinner synthesis, but that dichloro-, trichloro-, and nitroacetonitriles gave a mixture of the amide and imidate using

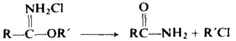
## TABLE I

### REACTION OF SUBSTITUTED NITRILES WITH ALCOHOLS TO GIVE IMIDATES

| RCN, R | R'OH, R' | Reaction conditions | | $\overset{NH_2Cl}{RC—OR}$ | | | $\overset{NH}{RC—OR'}$ | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Time (hr) | Temp. (°C) | Yield (%) | M.p., (°C) (dec.) | Yield (%) | B.p., °C (mm Hg) | $n_D$ (°C) | Ref. |
| $CH_3$ | $C_2H_5$ | 18 | 0–10 | 86.95 | — | — | — | — | *a* |
| $CH_3$ | $CH_3$ | 18 | 0–10 | 71.6 | — | — | — | — | *a* |
| $CH_3$ | $C_2H_5$ | 120 | 5 | — | — | 46 | 90 | 1.415 (24) | *b* |
| $C_4H_9$ | $C_2H_5$ | 120 | 5 | — | — | 64 | 61 (22) | 1.433 (20) | *b* |
| $C_2H_5$ | $C_2H_5$ | 120 | 5 | — | — | 60–65 | 65 (158) | 1.424 (20) | *b* |
| $C_3H_7$ | $C_2H_5$ | 120 | 5 | — | — | 65–70 | 75 (134) | 1.427 (19) | *b* |
| $(CH_3)_2$—CH | $C_2H_5$ | 120 | 5 | — | — | 75–80 | 75 (70) | 1.429 (21) | *b* |
| $C_5H_{11}$ | $C_2H_5$ | 120 | 5 | — | — | 80 | 77.5 (23) | 1.422 (22) | *b* |
| $(CH_3)_2CH$—$CH_2CH_2$ | $C_2H_5$ | 120 | 5 | — | — | 80 | 71 (20) | 1.420 (23) | *b* |
| $BrCH_2CH_2$ | $CH_3$ | 144 | 0–10 | 89.5 | 70.5–72 | — | — | — | *c* |
| $BrCH_2CH_2$ | $C_2H_5$ | 168 | 0–10 | 87 | 96.5–98.5 | — | — | — | *c* |
| $BrCH_2CH_2$ | $C_2H_5$ | 24 | 0–10 | 52 | 97.0–98.0 | — | — | — | *c* |
| $BrCH_2CH_2$ | *n*-$C_3H_7$ | 168 | 0–10 | 94.5 | 103–104 | — | — | — | *c* |
| $BrCH_2CH_2$ | *n*-$C_4H_9$ | 120 | 0–10 | 65 | 103–103.5 | — | — | — | *c* |
| $ClCH_2CH_2$ | $CH_3$ | 144 | 0–10 | 86 | 75.5–77.5 | — | — | — | *c* |
| $ClCH_2CH_2$ | $C_2H_5$ | 48 | 0–10 | 80 | 106–107 | — | — | — | *c* |
| $BrCH_2CH_2CH_2$ | $CH_3$ | 168 | 0–10 | 84 | — | — | — | — | *c* |
| $CNCH_2$ | $C_2H_5$ | 24 | 0–10 | 98 | 97 | 75–77 | 102–103 (10)<br>m.p. 78°–79°C | 1.501 (25) | *d* |
| $ClCH_2$ | $C_6H_5$ | 78 | 25 | 79 | 95–97 | — | — | — | *e* |
| $BrCH_2$ | $C_6H_5$ | 18 | 25 | 42 | 100–102 | — | — | — | *e* |
| $C_6H_5$ | $C_2H_5$ | 12 | 0–10 | 75 | — | 88 | 98–100 (2) | 1.5126 (20) | *f* |
| $C_6H_5$ | $CH_3$ | 4<br>72 | −5 to 0<br>0 | 64 | 103.5–104 | — | — | — | *g* |
| $C_6H_5CH_2$ | $CH_2$ | 24 | −10 | 94 | — | — | — | — | *h* |

[a] P. P. T. Sah, *J. Amer. Chem. Soc.* **50,** 516 (1928). [b] P. Reynaud and R. C. Moreau, *Bull. Soc. Chim. France* 2297 (1964). [c] J. P. Schroeder, D. C. Schroeder, J. Hardin, and J. K. Marshall, *J. Org. Chem.* **34,** 3362 (1969). [d] S. M. McElvain and J. P. Schroeder, *J. Amer. Chem. Soc.* **71,** 40 (1949). [e] S. M. McElvain and B. F. Pinzon, *J. Amer. Chem. Soc.* **67,** 690 (1945). [f] S. M. McElvain and C. L. Stevens, *J. Amer. Chem. Soc.* **68,** 1917 (1946). [g] A. J. Papa, *J. Org. Chem.* **35,** 2837 (1970). [h] J. P. Lokensgard, J. W. Fischer, and W. J. Bartz, *J. Org. Chem.* **50,** 5609 (1985). See also preparation 2-1 of this chapter for the related ethyl derivative.

aliphatic alcohols. Houben [38a] later found that aromatic alcohols gave the imidates with nitriles containing more than one negative substituent. McElvain and Nelson [41] have also shown that negative substituents enhance the tendency of imidate hydrochlorides to decompose to the corresponding amide and alkyl chloride (Eq. 23).

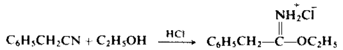


$$R{-}\overset{\overset{\displaystyle NH_2Cl}{\|}}{C}{-}OR' \longrightarrow R\overset{\overset{\displaystyle O}{\|}}{C}{-}NH_2 + R'Cl \qquad (23)$$

Recently [42a–e] it has shown that those nitriles which give poor yields under the acidic conditions of the Pinner synthesis give good yields under base-catalyzed conditions.

Table I gives many examples of the reaction of substituted nitriles with alcohols to give imidate hydrochlorides or imidates. The electronic and steric effect of aromatic nitriles on the yield of imidate hydrochloride is described in Table II. It is interesting to note that *ortho* chloro, sulfonamide, nitro, amino, and methyl groups retard the reaction whereas *ortho* ethoxy, hydroxy, or cyano groups do not hinder the reaction. In addition, acetylenic and olefinic groups do not hinder the reaction. The retarding steric effect is markedly shown by 1-cyanonaphthalene but 2-cyanonaphthalene reacts normally.

### 2-1. *Preparation of Ethyl Phenylacetimidate* [52]



$$C_6H_5CH_2CN + C_2H_5OH \xrightarrow{HCl} C_6H_5CH_2{-}\overset{\overset{\displaystyle \overset{+}{N}H_2\overset{-}{Cl}}{\|}}{C}{-}OC_2H_5 \qquad (24)$$

To an ice-cooled, round-bottomed flask containing a solution of 111.0 gm (0.90 mole) of benzyl cyanide in 48 gm (1.1 mole) of absolute ethanol is added 38.0 (1.04 mole) dry hydrogen chloride. The flask is stoppered and placed in a refrigerator for 12 hr and then an equal volume of dry ether is added.

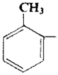
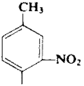
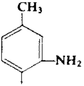
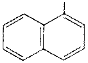
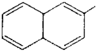
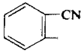
NOTE: If this mixture is allowed to stand for 2 weeks in the refrigerator the yield is increased to 83%.

The imidate hydrochloride that precipitates is filtered, washed with dry ether, and dried under reduced pressure over phosphorus pentoxide and sodium hydroxide to afford 136.0 gm (75%).

Neutralization [53] of the above imino hydrochloride is effected by adding the salt to an aqueous sodium bicarbonate solution and then immediately extracting into ether. The ether is removed by distillation and the residue is distilled under reduced pressure to afford 97.8 gm (88%) of

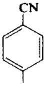
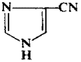
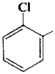
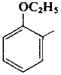
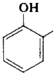
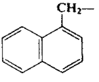
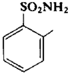
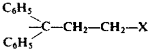
TABLE II

EXAMPLES OF THE EFFECT OF SUBSTITUENTS IN THE NITRILE COMPOUND ON THE YIELD OF THE CORRESPONDING IMIDATE HYDROCHLORIDE

| RCN, R = | Yields of imidate hydrochlorides | Ref. |
|---|---|---|
| OR′<br>$R' = C_6H_5$ or $o$-$CH_3—C_6H_4—$ | Poor | 1b |
| $—R'NH_2$ | Good | 43a,b |
| $C_6H_5C{\equiv}C—$ | Good | 44a,b |
| $—C_6H_4—C{=}C—(C_6H_5)_2$ | Good | 45 |
| $p$-$(CH_3OC_6H_4)_2C{=}C—C_6H_4—$ | Poor | 45 |
|  | Poor | 1b |
|  | Poor | 1b |
|  | Poor | 1b |
|  | Poor | 1b |
|  | Good | 46 |
|  | Good<br>(monoimidate salt only) | 47 |

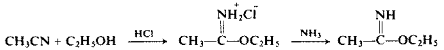
(*continues*)

TABLE II (*continued*)

| RCN, R = | Yields of imidate hydrochlorides | Ref. |
|---|---|---|
|  | Good | 47 |
|  | Good<br>(monoimidate salt only) | 22c |
|  | Very poor | 46 |
|  | Good | 48 |
|  | Good | 49 |
|  | Good | 37b |
|  | Poor | 50 |
|  $(C_6H_5)_2C{-}CH_2{-}CH_2{-}X$<br>X = Br, Cl | Poor | 51 |

ethyl phenyl-acetimidate, b.p. 97–100°C (2.0 mm Hg); $n_D^{20}$ 1.5126. This imidate is stable and shows no tendency to decompose into the nitrile and alcohol.

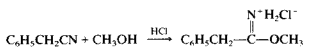
### 2-2. *Preparation of Ethyl Acetimidate* [54]



$$CH_3CN + C_2H_5OH \xrightarrow{HCl} CH_3-\overset{\overset{+}{N}H_2\overset{-}{Cl}}{\overset{\|}{C}}-OC_2H_5 \xrightarrow{NH_3} CH_3-\overset{NH}{\overset{\|}{C}}-OC_2H_5 \tag{25}$$

To a flask cooled to −5°C containing 61.5 gm (1.5 mole) of dry acetonitrile and 69.0 gm (1.5 mole) of anhydrous ethanol is added 532 gm (1.5 mole) of gaseous hydrogen chloride. The flask is stoppered and kept for 6 hr at 0°C and 4–5 days in the refrigerator. The resulting precipitate is filtered and washed with dry ether at 0°C. The salt is suspended in 500 ml of anhydrous ether and while stirring vigorously dry ammonia is passed into the suspension for 1.5 hr at −15°C. The resulting ammonium chloride is filtered and the ether solution is fractionally distilled to affect 60.0 gm (45.9%), b.p. 90°C, $n_D^{24}$ 1.415, $d_{23}$ 0.872.

### 2-3. *Preparation of Methyl Phenylacetimidate Hydrochloride* [35e]

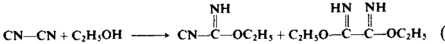


$$C_6H_5CH_2CN + CH_3OH \xrightarrow{HCl} C_6H_5CH_2-\overset{N^+H_2Cl^-}{\overset{\|}{C}}-OCH_3 \tag{26}$$

To a 50-ml pear-shaped flask equipped with a water-reflux condenser, a gas inlet tube reaching the bottom of the flask, and a gas outlet tube fitted with a drying tube is added 2.85 ml (2.90 g, 24.7 mmol) of phenylacetonitrile, 1.00 ml of dry methanol (0.80 g, 24.7 mmol) and 7 ml of anhydrous ether. The flask is cooled in an ice bath while dry hydrogen chloride gas (first passed through sulfuric acid) is passed into the solution until no more was absorbed.The flask is then disconnected, stoppered tightly, and stored at −10°C overnight. A solid forms, which is isolated by filtration under a stream of argon gas and then dried under reduced pressure for 4 hrs, to yield 4.30 g (23.2 mmol or 94% yield) of a white free-flowing powder. The NMR ($CDCl_3$, 90MHz) indicated 7.32 (m, 5H), 4.23 (s, 3H), 4.05 (s, 2H).

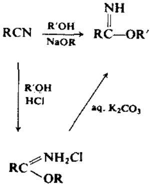
## B. Reaction of Nitriles with Alcohols in the Presence of Base

In 1895 Nef [55] reported that cyanogen reacted with an aqueous ethanol solution of potassium cyanide to give ethyl 1-cyanoformimidate and diethyl oxalimidate (Eq. 27). This reaction has recently been extended to other alcohols [56].



$$\mathrm{CN{-}CN + C_2H_5OH \longrightarrow CN{-}\overset{NH}{\overset{\|}{C}}{-}OC_2H_5 + C_2H_5O{-}\overset{HN}{\overset{\|}{C}}{-}\overset{NH}{\overset{\|}{C}}{-}OC_2H_5} \quad (27)$$

In 1896 Hesse [57] and in 1899 Hessler [58] reported a similarly easy base-catalyzed formation of imidates from substituted malonitriles. This reaction was further extended by Stieglitz [59a–d] and Acree [42a, 60] and their collaborators. Marshall and Acree [42a, 60] determined that several nitriles reacted with ethanol at 25°C in the presence of sodium ethoxide to give high conversions to imidates, In addition, they found that electron-attracting groups in the nitrile enhance its reactivity with alcohols when sodium ethoxide is used as the catalyst. Despite these and other earlier [61a–m] references, it remained for Schaefer and Peters [62] to establish that the base-catalyzed conversion of nitriles to imidates is a highly convenient preparative method. Most unsubstituted aromatic and aliphatic nitriles are ineffective in the base-catalyzed process, but can be used in the Pinner method to give imidates. In addition, nitriles which are very reactive in the base-catalyzed process usually give unstable imidate hydrochlorides in the Pinner synthesis. The two processes complement each other.



(28)

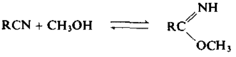
The base-catalyzed process has the additional advantage that the imidate is directly isolated by distillation and the excess nitrile is similarly recovered. Table III gives examples of the base-catalyzed process.

The preparation of polyimidates by the reaction of a hydroxynitrile such as ethylene cyanohydrin is discussed in Section 1.

Primary and secondary alcohols give high yields and most reactions are carried out at 25°C. Elevated temperatures tend to give lower yields. Table IV gives examples of the experimental conditions used in preparing imidates by the base-catalyzed reaction of nitriles with alcohols.

## TABLE III

### BASE-CATALYZED CONVERSION OF NITRILES TO METHYL IMIDATES[a]



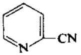
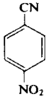
$$RCN + CH_3OH \rightleftharpoons RC(=NH)OCH_3$$

| Nitrile[b,c] | Time[d] (hr) | Conversion to imidate (%) | Nitrile[b,c] | Time[d] (hr) | Conversion to imidate (%) |
|---|---|---|---|---|---|
| $NCC(CH_3)_2C(CH_3)_2CN$[e] | 22 | 1[f] | $(C_2H_5O)_2CHCN$[n] | 1 | 95 |
| $NC(CH_2)_4CN$ | 24 | 1.5[f] | $p$-$CH_3OC_6H_4CN$ | 96 | 15 |
| $CH_3CN$ | 2 | 2 | $C_6H_5CN$ | 20 | 20 |
| $C_6H_5CH_2CN$ | 24 | 12 | $p$-$ClC_6H_4CN$ | 48 | 45 |
| $(C_2H_5)_2NCH_2CN$ | 48 | 22 | $p$-$NO_2C_6H_4CN$[o] | 8 | 83 |
| $NCCH_2CH_2CN$ | 24 | 69[g] | $m$-$NO_2C_6H_4CN$ | 4 | 86 |
| $C_4H_9OCH_2OCH(CH_3)CN$[h] | 96 | 86 | $p$-$C_6H_4(CN)_2$[p] | 7 | 108[g] |
| $[(C_2H_5)_3NCH_2CN]^+Cl^-$[i,j] | 48 | 76 | $3$-$C_5H_4NCN$ | 24 | 71 |
| $(CH_3)_3COCH_2CN$[k] | 30 | 91 | $2$-$C_5H_4NCN$ | 2 | 97 |
| $CH_2{=}CClCN$[l] | 24 | 90[m] | $(CH_3)_2NCN$ | 24 | 100[q] |
| $CH_3CHClCN$ | 0.5 | 91[m] | $(C_2H_5)_2NCN$ | 144 | 100[q] |
| $CH_2ClCN$ | 0.5 | 93[m] | | | |

[a] At 25°C. [b] Nitrile is 1.0 *M* except as noted; methanol is 21 *M* to 24 *M*. [c] Concentration of sodium methoxide catalyst is 0.1 *M* except as noted. [d] At least 95% of maximum imidate concentration was reached in the time given. [e] Nitrile, 0.38 *M*; sodium methoxide 0.042 *M*. [f] Conversion per nitrile group. [g] Conversion assuming one reactive nitrile group. [h] D. J. Loder and W. M. Bruner, U.S. Pat. 2,398,757 (1946). Nitrile, b.p. 119°C (50 mm Hg), $n_D^{20}$ 1.4082. [i] $(C_2H_5)_3N + Cl{-}CH_2CN \xrightarrow{25°C}$ 83% $(C_2H_5)_3N{-}CH_2CN + Cl$ (m.p. 190°–191°C from acetone). [j] Nitrile, 0.61 *M*; the catalyst was 0.10 *M* potassium cyanide. [k] Prepared as described by W. F. Gresham, U.S. Pat. 2,425,615 (1947). [l] Product is presumably methyl 2-chloro-3-methoxypropionimidate. K. Gundermann and H. Rose, *Chem. Ber.* 92, 1081 (1959). [m] These values are probably low because of loss of alkoxide through interaction with the reactive chloride. E. K. Marshall, Jr., and S. F. Acree, *Amer. Chem. J.* 49, 127 (1913). [n] J. G. Erickson, *J. Amer. Chem. Soc.* 73, 1338 (1951). [o] Nitrile, 0.95 *M*; sodium methoxide, 0.050 *M*. The nitrile dissolved completely in 6 hr. [p] Nitrile, 0.40 *M*; sodium methoxide, 0.10 *M*. The final solution was saturated with terephthalonitrile which was present in excess. [q] This reactivity of dialkylcyanamides was first reported by R. H. McKee, *Amer. Chem. J.* 26, 209 (1901). [Adapted from F. C. Schaefer and G. A. Peters, *J. Org. Chem.* 26, 412 (1960). Copyright 1961 by the American Chemical Society. Reprinted by permission of the copyright owners.]

TABLE

EXPERIMENTAL CONDITIONS FOR THE BASE-CATALYZED

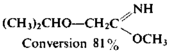
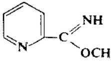
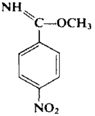
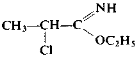
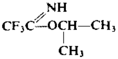
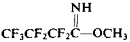
| RCN (moles) | ROH (moles) | Catalyst (moles) | Reaction condition: time (hr) |
|---|---|---|---|
| $(CH_3)_2CH{-}OCH_2CN$<br>(0.15) | $CH_3OH$<br>(1.24) | $NaOCH_3$<br>(0.01) | 18 |
| <br>(0.25) | $CH_3OH$<br>(5.58) | $NaOCH_3$<br>(0.025) | 18 |
| <br>(0.25) | $CH_3OH$<br>(2.48) | $NaOCH_3$<br>(0.0185) | 4 |
| <br>$CH_3{-}\underset{Cl}{CH}{-}CN$<br>(0.73) | $C_2H_5OH$<br>(4.96) | $NaOCH_3$<br>(0.040) | 3/4 |
| $CF_3CN$<br>(0.10) | $(CH_3)_2CHOH$<br>(0.15) | $(CH_3)_3N$[b]<br>(0.01) | 72<br>24 |
| $CF_3CF_2CF_2CN$<br>(0.23) | $CH_3OH$<br>(0.74) | $NaOCH_3$<br>(0.00174) | 1<br>1 |

---

[a] F. C. Schaefer and G. A. Peters, *J. Org. Chem.* **26**, 412 (1961). [b] Reaction carried out in a glass ampoule. [c] H. C. Brown and C. R. Wetzel, *J. Org. Chem.* **30**, 3724 (1965);

IV

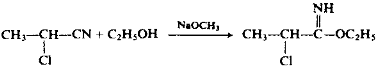
REACTION OF NITRILES WITH ALCOHOLS TO GIVE IMIDATES[a]

| Reaction condition: temp. (°C) | Product | Yield (%) | B.p., °C (mm Hg) or m.p., °C | Ref. |
|---|---|---|---|---|
| 25 |  $(CH_3)_2CHO{-}CH_2C({=}NH)OCH_3$<br>Conversion 81% | 60 | 32–37 (2) | *a* |
| 25 |  | 90 | 118–122 (28) | *a* |
| 66 |  | 63 | 75 | *a* |
| 25 |  $CH_3{-}CHCl{-}C({=}NH)OC_2H_5$ | 51 | 70–75 (60) | *a* |
| 25<br>70 |  $CF_3C({=}NH){-}OCH(CH_3){-}CH_3$ | 89 | 65.5–67<br>($n_D^{25}$ 1.3225) | *b,c* |
| < 60<br>25 |  $CF_3CF_2CF_2C({=}NH){-}OCH_3$ | 87 | 75–76<br>($n_D^{25}$ 1.3065) | *c,d* |

---

[d] E. L. Zaitseva, R. M. Gitina, A. Y. Yakubovich, G. J. Braz, L. G. Petrova, and V. P. Bazov, *Zh. Obshch. Khim.* **34,** 2816 (1964).

### *2-4. Preparation of Ethyl 2-Chloropropionimidate* [62]

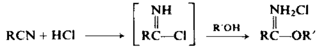


$$\mathrm{CH_3{-}\underset{\displaystyle Cl}{\underset{|}{C}}H{-}CN + C_2H_5OH \xrightarrow{NaOCH_3} CH_3{-}\underset{\displaystyle Cl}{\underset{|}{C}}H{-}\overset{\displaystyle NH}{\overset{\|}{C}}{-}OC_2H_5} \tag{29}$$

To a flask containing 65.0 gm (0.83 mole) of 2-chloropropionitrile dissolved in 200 ml of absolute ethanol is added 2.2 gm (0.040 mole) of sodium methoxide. The reaction is slightly exothermic and cooling is necessary to keep the temperature at 25°C. After 45 min, 2.4 ml (0.040 mole) of glacial acetic acid is added and the resulting solution is distilled under reduced pressure to afford 53 gm (51%), b.p. 70–75°C (60 mm Hg). The purity is approximately 95% imidate by titration.

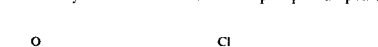
## C. Synthesis of Imidates via Imino Chlorides

The Pinner synthesis may involve the intermediate formation of imino chloride which subsequently reacts with alcohols (Eq. 30).



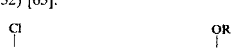
$$\mathrm{RCN + HCl \longrightarrow \left[R\overset{\displaystyle NH}{\overset{\|}{C}}{-}Cl\right] \xrightarrow{R'OH} R\overset{\displaystyle NH_2Cl}{\overset{\|}{C}}{-}OR'} \tag{30}$$

N-substituted imino chlorides are stable [63] and can be easily prepared by reaction of *N*-aryl-substituted amides with phosphorus pentachloride (Eq. 31).



$$\mathrm{Ar{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}NHAr + PCl_5 \longrightarrow Ar{-}\overset{\displaystyle Cl}{\overset{|}{C}}{=}N{-}Ar + HCl + POCl_3} \tag{31}$$

[64]. After removing the phosphorus oxychloride the imino chlorides can either be isolated or directly reacted with alkoxides or phenoxides to give the imidates (Eq. 32) [65].

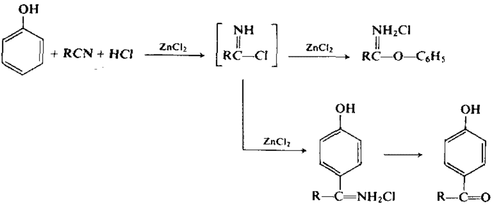


$$\mathrm{Ar\overset{\displaystyle Cl}{\overset{|}{C}}{=}N{-}Ar + RONa \longrightarrow Ar{-}\overset{\displaystyle OR}{\overset{|}{C}}{=}NAr} \tag{32}$$

Several examples wherein substituted phenols are reacted with benzanilimino chloride to give imidates (benzanilimino ethers) are shown in Table V.

The use of thiophenoxides gives N-substituted thioimidates [66].

The Hoesch [67] synthesis (Eq. 33) may also proceed via an imino chloride intermediate to give in some cases isolatable imidate hydrochlorides.



(33)

## 2-5. *General Procedure for the Preparation of Imidates from Benzanilimino Chlorides and Substituted Phenols* [68a]

To a dry flask containing 250 ml of ethanol and 0.3 mole of the phenol is added 5.8 gm (0.25 mole) of small portions of sodium metal. After the reaction is complete, 50.0 gm (0.24 mole) of benzanilimino chloride in

TABLE V

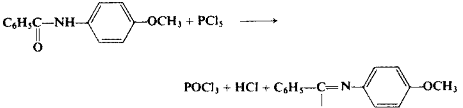
PREPARATION OF IMIDATES BY THE REACTION OF BENZANILIMINO CHLORIDE WITH SUBSTITUTED PHENOLS

| | Yield | Melting point (°C) | | | Yield | Melting point (°C) | |
|---|---|---|---|---|---|---|---|
| Substituent | (%) | Found | Reptd. | Substituent | (%) | Found | Reptd. |
| Unsubst. | 64 | 104.2–105.0 | 105 | *o*-Cl | 37 | 85.7–86.1 | 88 |
| *o*-$CH_3$ | 46 | 73.4–73.8 | — | *p*-Cl | 57 | 90.0–90.6 | 92–93 |
| *m*-$CH_3$ | 60 | 62.7–63.2 | 65 | *p*-Br | 51 | 83.0–83.8 | — |
| *p*-$CH_3$ | 64 | 58.8–59.8 | — | *p*-$CH_3CO$ | 45 | 94.4–94.9 | 94–95 |
| *o*-$C_2H_5$[c] | — | — | — | *o*-$NO_2$[a,b,d] | 54 | 109.6–112 | 116 |
| *p*-$C_2H_5$ | 15 | 42.7–43.3 | — | *p*-$NO_2$[a,b,d] | 30 | 73.0–73.8 | 76–77 |
| *o*-*i*-$C_3H_7$[b] | 58 | 76.2–76.7 | — | *o*-$CH_3O$ | 20 | 112.6–112.8 | 113 |
| *p*-*i*-$C_3H_7$ | 39 | 65.3–65.8 | — | *p*-$CH_3O$ | 66 | 77.4–78.4 | 79–80 |
| *o*-*t*-$C_4H_9$ | 40 | 90.7–91.1 | — | *p*-*p*′-diCl | 60 | 65.7–66.5 | 68–69 |
| *p*-*t*-$C_4H_9$ | 57 | 97.2–97.6 | — | | | | |

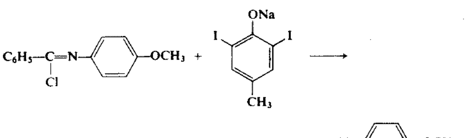
[a] The substituted phenol was added after all of the sodium had reacted.
[b] *t*-Butyl alcohol was used as the solvent instead of absolute ethanol.
[c] *It was not possible to obtain this compound in crystalline form.*
[d] These compounds were found not to give clean reactions, and thus were not studied further.
[Reprinted in part from K. B. Wiberg and B. I. Rowland, *J. Amer. Chem. Soc.* **77**, 2205 (1955). Copyright 1955 by the American Chemical Society. Reprinted by permission of the copyright owner.]

50 ml of absolute ether is added. After 15 hr, the solution is distilled until 175 ml of distillate is collected. The residue is poured into 500 ml of ice water and after 18 hr the solid product is filtered. The product is recrystallized from absolute ethanol and the results are as shown in Table V.

### 2-6. *Preparation of 2,6-Diiodo-4-methylphenyl N-p-Methoxyphenylbenzimidate* [65]



(34)

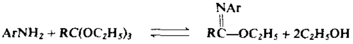


(35)

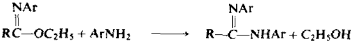
To a flask containing 25.0 gm (0.11 mole) of benzanisidide is added 23.0 gm (0.11 mole) of phosphorus pentachloride and the flask is warmed on the steam bath until no more hydrogen chloride is evolved. The phosphorus oxychloride is removed using an aspirator and the imidoyl chloride which crystallizes on cooling is added to 75 ml of dioxane. The latter solution is added to a solution of 61.0 gm (0.16 mole) of diiodo-*p*-cresol in 150 ml of ethanol prereacted with 2.8 gm (0.11 gm-atom) of sodium metal. The resulting sodium chloride precipitate is filtered and the ester crystallizes out. The product is washed with alcohol and water to afford 47.0 gm (75%), m.p. 158–160°C (recrystallized from alcohol-dioxane).

## D. Synthesis of Imidates from Ortho Esters

Aromatic amines react with ortho esters to give alkyl *N*-arylimidic esters (Eq. 36) [68a,b]. The use of excess amine leads to amidine formation (Eq. 37).



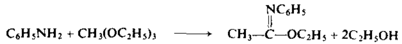
$$ArNH_2 + RC(OC_2H_5)_3 \rightleftharpoons R\overset{NAr}{\overset{\|}{C}}{-}OC_2H_5 + 2C_2H_5OH \qquad (36)$$



$$R\overset{NAr}{\overset{\|}{C}}{-}OC_2H_5 + ArNH_2 \longrightarrow R{-}\overset{NAr}{\overset{\|}{C}}{-}NHAr + C_2H_5OH \qquad (37)$$

[68b]. Acid catalysts are not required, as is true in preparing *N*-arylformimidic esters [68c] by an analogous reaction. Table VI gives several examples of this reaction. This reaction is also applicable to other ortho esters and sterically hindered amines.

### 2-7. *Preparation of Ethyl* N-*Phenylacetimidate* [69a]



$$C_6H_5NH_2 + CH_3(OC_2H_5)_3 \longrightarrow CH_3{-}\overset{NC_6H_5}{\overset{\|}{C}}{-}OC_2H_5 + 2C_2H_5OH \qquad (38)$$

To a flask equipped with a distillation column and distillation head is added 23.2 gm (0.25 mole) of aniline and 45.4 gm (0.28 mole) of triethyl orthoacetate. The reaction mixture is heated and ethanol is distilled off as it is formed until 23 gm (0.50 mole) is collected. The reaction mixture is cooled and then distilled under reduced pressure to afford 40.8 gm (74%), b.p. 94.5°C (12.5 mm Hg), $n_D^{25}$ 1.5167, $d_4^{25}$ 0.986.

Amines other than aniline are capable of undergoing the reaction with ortho esters to give imidates. For example, *N*-cyanoimidates have been prepared by the reaction of cyanamide with ortho esters, as shown in Table VII [69b].

A similar reaction has been used by Whitehead and Traverso to convert ureas to *N*-carbamoylimidates [70].

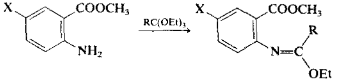
More recently, Leiby reported on a general procedure for the preparation of *N*-(2-Carboxymethoxyphenyl) imidate esters by the reaction of methyl orthranilate with excess ortho ester [70b]. Preparation 2-8 and Table VIII give examples of the latter procedure.

TABLE VI
REACTION OF AROMATIC AMINES WITH ORTHO ESTERS TO GIVE *N*-ARYLACETIMIDIC ESTERS[a]

| $R—NH_2$ (0.25 mole), R = | $CH_3C(OC_2H_5)_3$ except where noted (moles) | Yield of imidate (%) | B.p., °C (mm Hg) | $n_D^{25}$ | $d_4^{25}$ |
|---|---|---|---|---|---|
| $C_6H_5$– | 0.28 | 74 | 94.5<br>(12.5) | 1.5167 | 0.986 |
| *o*-$CH_3$—$C_6H_4$– | 0.28 | 94 | 104–105<br>(13.0) | 1.5121 | 0.968 |
| *m*-$CH_3$—$C_6H_4$– | 0.28 | 87 | 116–117<br>(11.3) | 1.5147 | 0.968 |
| *p*-$CH_3$—$C_6H_4$– | 0.28 | 87 | 111–112<br>(13.3) | 1.5151 | 0.977 |
| *o*-Cl—$C_6H_4$ | 0.28 | 77 | 119–120<br>(16.2) | 1.5289 | 1.105 |
| *m*-Cl—$C_6H_4$ | 0.28 | 90 | 121–123<br>(12.9) | 1.5318 | 1.101 |
| *p*-Cl—$C_6H_4$– | 0.28 | 95 | 123–124<br>(11.8) | 1.5323 | 1.103 |
| *o*-$C_2H_5O$—$C_6H_4$– | 0.28 | 88 | 127.5–128.5<br>(13.5) | 1.5129 | 1.008 |
| *p*-$C_2H_5O$—$C_6H_4$– | 0.28 | 92 | 146–147<br>(15) | 1.5181 | 1.018 |
| 2,6-$(C_2H_5)_2$—$C_6H_3$– | 0.28 | 91 | 109–110<br>(6.3) | 1.5084 | 0.946 |
| 3,4-$(Cl)_2$—$C_6H_3$– | 0.28 | 95 | 110.5–111<br>(0.99) | 1.5487 | 1.221 |
| $C_6H_5$–<br>(0.20) | $CH_3CH_2C(OC_2H_5)_3$<br>0.23 | 92.5 | 104–105<br>(12.5) | 1.5099 | 0.969 |
| 2,6-$(C_2H_5)_2C_6H_3$–<br>(0.25) | $CH(OC_2H_5)_3$<br>0.30 | 90 | 146–147.5<br>(26) | 1.5079 | 0.958 |

[a] Data taken from R. H. DeWolfe, *J. Org. Chem.* **27**, 490 (1962).

## 2-8. *General Procedure for the Preparation of* N-(2-Carbomethoxyphenyl) *Imidate Esters* [70b]



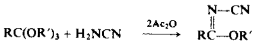
(39)

(I) (II) (III)

A solution of (I) was reacted with an excess of the ortho ester (II) while stirring and heating at reflux for a specific amount of time. The solution is

## TABLE VII

### PREPARATION OF *N*-CYANOIMIDATES FROM CYANAMIDE AND ORTHO ESTERS



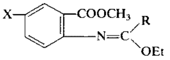
$$RC(OR')_3 + H_2NCN \xrightarrow{2Ac_2O} R\overset{\overset{N-CN}{\|}}{C}-OR'$$

| R = | R′ = | Temp. (°C) | Time | Yield (%) | B.p., °C (mm Hg) |
|---|---|---|---|---|---|
| $CH_3$ | $C_2H_5$ | 140 | 1 hr | 90 | 90–95 (20) |
| H | $C_2H_5$ | 140 | 1 hr | 90 | 58–63 (0.1) |
| $C_2H_5O_2CCH_2$[a] | $C_2H_5$ | 150 | 15 min | 74 | 103–106 (0.2) |
| $C_6H_5$ | $CH_3$ | 150 | 20 min | 61 | 115–125 (0.3) |
| $ClCH_2$ | $CH_3$ | 130 | 30 min | 75 | 76–80 (0.3) |
| $ClCH_2$ | $C_2H_5$ | 145 | 30 min | 65 | 87–90 (0.2) |

[a] The ketene acetal was used with one equivalent of acetic anhydride. [Reprinted from K. R. Huffman and F. C. Schaefer, *J. Org. Chem.* **28**, 1816 (1963). Copyright 1963 by the American Chemical Society. Reprinted by permission of the copyright owner.]

## TABLE VIII

### *N*-(2-CARBOMETHOXYPHENYL)IMIDATE ESTERS PREPARED BY PREPARATION 2-8 [70b][a]

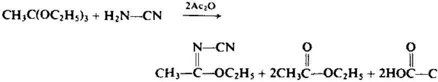


| X | R | Reactant ratio (2/1) | Reflux time (hr) | % Yield | B.p. °C (mm Hg) |
|---|---|---|---|---|---|
| H | H | 1.5 | — | 45 | 91 (0.1) |
| H | H | 2.0 | 48 | 38.4 | 135–138 (6.0) |
| H | $CH_3$ | 1.3 | 32 | 70.1 | 80–84 (0.25) |
| H | $C_2H_5$ | 1.3 | 48 | 88.8 | 124–125 (1.00) |
| Cl | H | 24.0 | 72 | 66.7 | 110–111 (0.45) |
| Cl | $CH_3$ | 2.8 | 72 | 90.2 | 108.0–108.5 (0.25) |
| Cl | $C_2H_5$ | 4.4 | 65 | 83.6 | 134–136 (1.30) |
| Br | $CH_3$ | 4.6 | 72 | 93.6 | 128–129 (0.45) |
| Br | $C_2H_5$ | 3.7 | 72 | 85.6 | 118–119 (0.3) |

[a] R. W. Leiby, *J. Org. Chem.* **50**, 2926 (1985).

allowed to cool, and the unreacted orthoester and formed ethanol were removed under reduced pressure. The residue is then distilled under reduced pressure, to give (III) the imidate ester (NMR). The imidate was identified by means of the infrared spectra. For example, the analysis for methyl-*N*-(2-carbomethoxyphenyl) acetimidate follows: IR (neat) 1740 (C═O), 1680 (C═N), 1235 and 1280 cm$^{-1}$ (C—O) NMr (Neat), $\delta$ 1.25 (*t*, 3, $CH_2CH_3$), 1.70 (*s*, 3, N═C-$CH_3$), 3.70 *S*, 3, $OCH_3$), 4.25 (*q*, 2, $CH_2CH_3$), 6.69 (*dd* J = 2 and 8 Hz, 1, $ArH_6$) 6.91 (*td*, J = 2 and 7 Hz, 1, Ar $H_4$); 7.31 (*td*, J = 2 and 7 Hz, Ar $H_5$), 7.85 (*dd*, J = 2 and 8 Hz, 1 Ar $H_3$). For additional examples see Table VIII.

### *2-9. Preparation of Ethyl* N*-Cyanoacetimidate* [69b]



$$CH_3C(OC_2H_5)_3 + H_2N{-}CN \xrightarrow{2Ac_2O} CH_3{-}\overset{N-CN}{\overset{\|}{C}}{-}OC_2H_5 + 2CH_3\overset{O}{\overset{\|}{C}}{-}OC_2H_5 + 2HO\overset{O}{\overset{\|}{C}}{-}CH_3 \qquad (40)$$

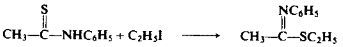
To a flask equipped as in Preparation 2-6 is added 162.0 gm (1.0 mole) of ethyl orthoacetate, 42.0 gm (1.0 mole) of cyanamide [71], and 134.0 gm (2.0 moles) of acetic anhydride. The reaction mixture is heated to 130–140°C and the ethyl acetate and acetic acid are distilled over. The heat is removed until the initial vigorous reaction subsides and then the heating is continued at 135–140°C until most of the remaining ethyl acetate and acetid acid have distilled over (approx. 1 hr). The residue is then distilled under reduced pressure to afford 100.8 gm (90%), b.p. 90–95°C (20 mm Hg).

Ortho esters also react with a variety of other amino derivatives such as *o*-aminobenzenesulfonamides, thiosemicarbazide, carboxylic hydrazides, urea, and *N*-alkylureas to give the products shown in Scheme 1.

## E. Direct Alkylation of Amides

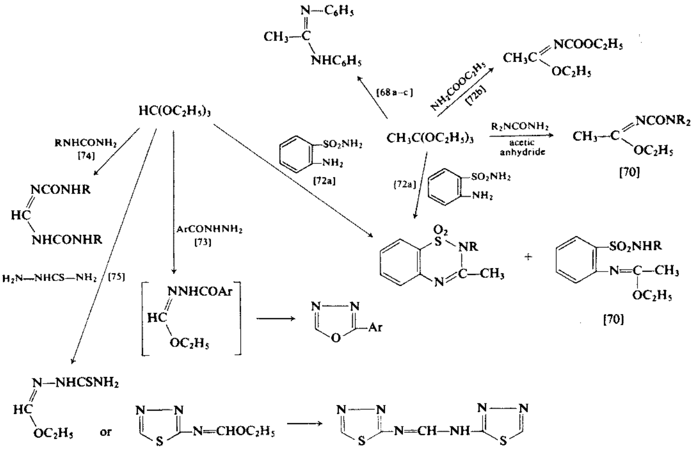
### a. Reaction of Amides with Active Halides

Thioamides [76a–h] and thioureas [77] react with active halides such as ethyl iodide, chloroacetic acid, *p*-nitrobenzoyl chloride, and benzyl chloride to give imidate salts in quantitative yield (Eqs. 41–45). (See Table IX.)



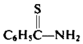
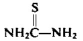
$$CH_3{-}\overset{S}{\overset{\|}{C}}{-}NHC_6H_5 + C_2H_5I \longrightarrow CH_3{-}\overset{NC_6H_5}{\overset{\|}{C}}{-}SC_2H_5 \qquad (41)$$

SCHEME 1
Reaction of Ortho Esters with Amino Derivatives



## TABLE IX

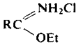
### Reaction of Thioamides with Halides to Give Thiomidate Hydrochlorides

| Amide | Halide | Yield (%) | M.p. (°C) | Ref. |
|---|---|---|---|---|
|  $C_6H_5\overset{\overset{S}{\|}}{C}{-}NH_2$ | $Cl{-}CH_2COOH$ | 100 | 124–125 | *a* |
|  $NH_2\overset{\overset{S}{\|}}{C}{-}NH_2$ | $Cl{-}CH_2C_6H_5$ | 100 | 172–174 | *b* |

[a] W. M. Lauer and G. W. Lones, *J. Amer. Chem. Soc.* 59, 232 (1937). [b] J. J. Donleavy, *J. Amer. Chem. Soc.* **58**, 1004 (1936).

## TABLE X

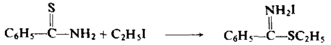
### Imidate Hydrochlorides



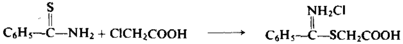
$RC{\overset{\textstyle NH_2Cl}{\underset{\textstyle OEt}{}}}$

| R = | RCONH₂ + EtOCOCl M.p.[a] (°C) | RCONH₂ + EtOCOCl Yield (%) | RCN + EtOH + HCl M.p.[a] (°C) | RCN + EtOH + HCl Yield (%) | Lit. m.p. (°C) |
|---|---|---|---|---|---|
| $CH_3$ | 113 | 32 | 112–113 | 54 | 98–100[b] |
| $CH_3CH_2$ | 92–93 | 65 | 93–94 | 36 | 90–92[b] |
| $CH_3(CH_2)_2$ | 64–65 | 83 | 56–58 | 48 | 64–65[b] |
| $(CH_3)_2CH$ | 89 | 68 | 83 | 85 | 76[c] |
| $CH_3(CH_2)_3$ | Liq[d] | 72 | Liq[d] | 62 | — |
| $(CH_3)_2CHCH_2$ | 88–89 | 75 | 89–90 | 47 | 90[c] |
| $CH_3(CH_2)_4$ | Liq[d] | 75 | Liq[d] | 63 | Liq[c] |
| $(CH_5)_2CH(CH_2)_2$ | Liq[d] | 80 | Liq[d] | 67 | Liq[e] |
| $CH_3(CH_2)_5$ | Liq[d] | 75 | Liq[d] | 45 | 67[f] |
| $CH_3(CH_2)_6$ | Liq[d] | 88 | 34 | 55 | — |

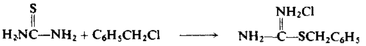
[a] Really decomposition temperature; melting is accompanied by gas evolution. [b] A. Pinner, "Die Imidoaether and ihre Derivative," pp. 1–85. Oppenheim, Berlin, 1892. [c] N. S. Drozdov and A. F. Bekhli, *J. Gen. Chem. USSR* **14**, 280 (1944). [d] A viscous syrup at room temperature, which crystallized on storing at 0°C, but remelted on return to room temperature. [e] A. Pinner, *Chem. Ber.* **17**, 171 (1884). [f] A. Pinner, *Chem. Ber.* **28**, 473 (1895). [Reprinted from F. H. Suydam, W. E. Greth, and N. R. Langerman, *J. Org. Chem.* 34, 292 (1969). Copyright 1969 by The American Chemical Society. Reprinted by permission of the copyright owner.]



$$\mathrm{C_6H_5}-\overset{\overset{\mathrm{S}}{\|}}{\mathrm{C}}-\mathrm{NH_2} + \mathrm{C_2H_5I} \longrightarrow \mathrm{C_6H_5}-\overset{\overset{\mathrm{NH_2I}}{\|}}{\mathrm{C}}-\mathrm{SC_2H_5} \qquad (42)$$

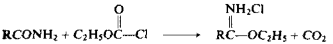


$$\mathrm{C_6H_5}-\overset{\overset{\mathrm{S}}{\|}}{\mathrm{C}}-\mathrm{NH_2} + \mathrm{ClCH_2COOH} \longrightarrow \mathrm{C_6H_5}-\overset{\overset{\mathrm{NH_2Cl}}{\|}}{\mathrm{C}}-\mathrm{SCH_2COOH} \qquad (43)$$



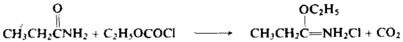
$$\mathrm{H_2N}\overset{\overset{\mathrm{S}}{\|}}{\mathrm{C}}-\mathrm{NH_2} + \mathrm{C_6H_5CH_2Cl} \longrightarrow \mathrm{NH_2}-\overset{\overset{\mathrm{NH_2Cl}}{\|}}{\mathrm{C}}-\mathrm{SCH_2C_6H_5} \qquad (44)$$

Primary and secondary aliphatic amides react with ethyl chloroformate in the absence of solvent at temperatures below 50°C to give imidate hydrochlorides in good yields (Eq. 45). For comparison, Table X shows the yields of imidate hydrochlorides obtained by the above procedure and by the Pinner method. Attempts to react benzamide, *p*-nitrobenzamide, or $\alpha$-phenylacetamide with ethyl chloroformate failed. At the present time it appears that this procedure may only be limited to aliphatic amides (Eq. 45).



$$\mathrm{RCONH_2} + \mathrm{C_2H_5O}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{Cl} \longrightarrow \mathrm{R}\overset{\overset{\mathrm{NH_2Cl}}{\|}}{\mathrm{C}}-\mathrm{OC_2H_5} + \mathrm{CO_2} \qquad (45)$$

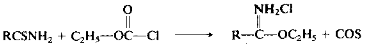
### *2-10. Preparation of Ethyl Propionimidate Hydrochloride*



$$\mathrm{CH_3CH_2}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{NH_2} + \mathrm{C_2H_5OCOCl} \longrightarrow \mathrm{CH_3CH_2}\overset{\overset{\mathrm{OC_2H_5}}{|}}{\mathrm{C}}{=}\mathrm{NH_2Cl} + \mathrm{CO_2} \qquad (46)$$

To a 250-ml round-bottomed, three-necked flask equipped with mechanical stirrer, dropping funnel, and condenser with a top outlet tube extending into a saturated barium hydroxide solution is added 7.3 gm (0.10 mole) of propionamide. The flask is placed in a water bath at 40–45°C while 10.9 gm (0.10 mole) of ethyl chloroformate is added rapidly from the dropping funnel. The reaction mixture is rapidly stirred and in 15 min the reaction commences with the evolution of $CO_2$ as evidenced by precipitation in the $Ba(OH)_2$ solution. After the carbon dioxide ceases to be evolved the product is washed with anhydrous ether and dried in a vacuum desiccator over conc. sulfuric acid to afford 8.9 gm (65%), m.p. 92–93°C.

The reaction of ethyl chloroformate with *N*-methyl or *N*-ethyl alkylamides afforded the corresponding *N*-alkyl imidate hydrochloride, a class of compounds for which no other direct method of synthesis exists (see Table X). The reaction fails with acetanilide, *n*-butylacetamide, *N*-methylacetamide, and *N*-methylcaprylamide. However, thiobenzamide and thioacetanilide each react with ethyl chloroformate to give ethyl benzimidate hydrochloride and ethyl *N*-phenylacetaimidate hydrochloride, respectively (Eq. 47).

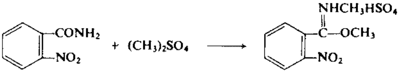


$$RCSNH_2 + C_2H_5{-}O\overset{\overset{O}{\|}}{C}{-}Cl \longrightarrow R{-}\overset{\overset{NH_2Cl}{\|}}{C}{-}OC_2H_5 + COS \qquad (47)$$

A procedure similar to that of Preparation 2-7 is used for the preparation of the *N*-substituted imidate hydrochlorides shown in Table XI except that dry petroleum ether (b.p. 30–60°C) is used for washing the products rather than ethyl ether, in which the products are very soluble. All the products are liquids which tend to decompose upon attempted distillation.

### b. REACTION OF AMIDES WITH DIALKYL SULFATES

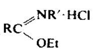
Amides and thioamides also react with dimethyl sulfate [79a–c] to give methyl hydrogen sulfate salts of the imidates or thioimidates (Eqs. 48, 49). Alkylation of urea with dimethyl sulfate affords pseudoureas [80].



(48)

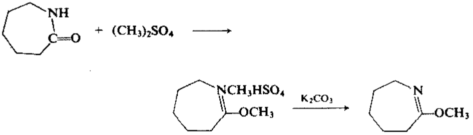
TABLE XI

IMIDATE HYDROCHLORIDES[a]

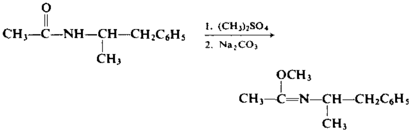


| R = | R′ = | Yield (%) | R = | R′ = | Yield (%) |
|---|---|---|---|---|---|
| H | $CH_3$ | 88 | $CH_3(CH_2)_3$ | $CH_3CH_2$ | 69 |
| H | $CH_3CH_2$ | 92 | $CH_3(CH_2)_4$ | $CH_3$ | 73 |
| $CH_3$ | $CH_3CH_2$ | 78 | $CH_3(CH_2)_4$ | $CH_3CH_2$ | 77 |
| $CH_3CH_2$ | $CH_3$ | 67 | $CH_3(CH_2)_5$ | $CH_3CH_2$ | 84 |
| $CH_3CH_2$ | $CH_3CH_2$ | 75 | $CH_3(CH_2)_5$ | $CH_3$ | 44 |
| $CH_3(CH_2)_2$ | $CH_3$ | 80 | $CH_3(CH_2)_6$ | $CH_3CH_2$ | 74 |
| $CH_3(CH_2)_2$ | $CH_3CH_2$ | 76 | | | |

[a] Additional evidence for identification of the compounds was obtained by hydrolysis of each compound to the corresponding aniline hydrochloride and ester, and comparison of their infrared spectra with those of authentic samples. [Adapted from F. H. Suydam, W. E. Greth, and N. R. Langerman, *J. Org. Chem.* 34, 292 (1969). Copyright 1969 by the American Chemical Society. Reprinted by permission of the copyright owner.]


(49)

## 2-11. *Preparation of Methyl N-(α-Methylphenethyl)acetimidate* [81]

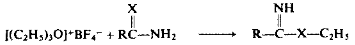


$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-NH-\underset{\underset{\displaystyle CH_3}{|}}{CH}-CH_2C_6H_5 \xrightarrow[\text{2. } Na_2CO_3]{\text{1. } (CH_3)_2SO_4} CH_3-\overset{\overset{\displaystyle OCH_3}{|}}{C}=N-\underset{\underset{\displaystyle CH_3}{|}}{CH}-CH_2C_6H_5 \qquad (50)$$

To a dry flask is added 8.1 gm (0.045 mole) of *N*-(α-methylphenethyl)-acetamide and 5.7 gm (0.045 mole) of dimethyl sulfate. The mixture is heated for 2 hr at 100–105°C, cooled, washed by decantation with ether, and the oily residue covered with fresh ether and shaken with 30% aqueous sodium carbonate. The resulting ether layer is dried over magnesium sulfate, concentrated, and the residual oil dissolved in petroleum ether (b.p. 30–60°C). The resulting precipitate of unreacted amide is filtered and the residue distilled under reduced pressure to afford 5.8 gm (67%), b.p. 60°C (0.7 mm Hg); $n_D^{25}$ 1.4948.

### c. REACTION OF AMIDES WITH TRIETHYLOXONIUM TETRAFLUOROBORATE

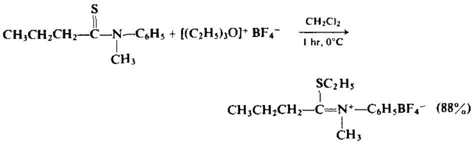
Recently triethyloxonium tetrafluoroborate has been used to react with thioamides [82] and amides [83] to give imidates (Eq. 51).



$$[(C_2H_5)_3O]^+BF_4^- + R\overset{\overset{\displaystyle X}{\|}}{C}-NH_2 \longrightarrow R-\overset{\overset{\displaystyle NH}{\|}}{C}-X-C_2H_5 \qquad (51)$$

X = O or S

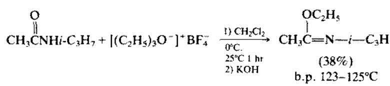
This method appears to be promising and a further investigation of its general utility has yet to be carried out. Its major disadvantage is that triethyloxonium tetrafluoroborate is not commercially available [84]. A typical example [83] of this method is shown in (Eq. 52).



$$CH_3CH_2CH_2-\overset{\overset{S}{\|}}{C}-\underset{\underset{CH_3}{|}}{N}-C_6H_5 + [(C_2H_5)_3O]^+BF_4^- \xrightarrow[1\ hr,\ 0°C]{CH_2Cl_2} CH_3CH_2CH_2-\overset{\overset{SC_2H_5}{|}}{C}=\underset{\underset{CH_3}{|}}{N^+}-C_6H_5BF_4^- \quad (88\%)$$

(52)

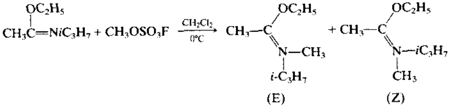
Another example of its use is the preparation of ethyl *N*-isopropylacetimidate as shown in Eq. 53 [83b].



$$CH_3\overset{\overset{O}{\|}}{C}NHi\text{-}C_3H_7 + [(C_2H_5)_3O^-]^+BF_4^- \xrightarrow[\substack{0°C.\\ 25°C\ 1\ hr\\ 2)\ KOH}]{1)\ CH_2Cl_2} CH_3\overset{\overset{OC_2H_5}{|}}{C}=N-i-C_3H_7 \quad (53)$$

(38%)
b.p. 123–125°C

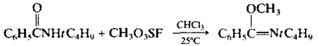
The latter compound has been reported to be able to react with methyl fluorosulfonate to give *N*-methyl-*N*-isopropylimidate salt, as a 1 : 1 mixture of E and Z isomers.



(E) (Z)
m.p. 70–80°C

(54)

### 2-12. *Preparation of Methyl* N-tert-*Butylbenzimidate*

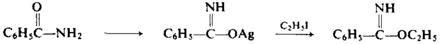


$$C_6H_5\overset{\overset{O}{\|}}{C}NHtC_4H_9 + CH_3O_3SF \xrightarrow[25°C]{CHCl_3} C_6H_5\overset{\overset{OCH_3}{|}}{C}=NtC_4H_9 \quad (55)$$

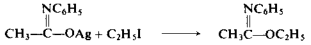
To a flask containing 79.0 g (0.446 mole) of *N-t*-butylbenzamide was added 200 ml chloroform to prepare a solution. Then 150 g (1.27 mole) of methyl fluorosulfonate was added at room temperature and then stirred for 24 hr. Concentration under reduced pressure gave a white solid. The solid was dissolved in 300 ml of methylene chloride and then neutralized with 200 ml of ice-cold 10% sodium hydroxide. The solution containing the product was dried over sodium hydroxide, then concentrated to give the product, which was distilled to give 46.5 g (54.6%) of methyl *N-tert*-butylbenzimidate, b.p. 56°C (2.5 Torr.). The IR (neat) $cm^{-1}$ 3035 (w), 2980 (s), 1675 (s), 1600 (w), 1390 (s), 1358 (s), 1270 (s), 1200 (m), 700 (m). NMR H' ($CDCl_3$): $\delta$ 1.21 (s, 9H, Nt-Bu), 3.62 (s, 3H, $OCH_3$), 7.35 (s, 5H ArH).

d. REACTION OF AMIDE–SILVER-OXIDE ADDUCTS WITH ALKYL IODIDES

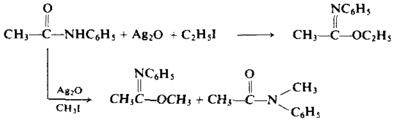
The silver salts of amides [85a–c] and anilides [86a–d] react with ethyl iodide to give imidates [56–58]. In the case of the amide, using methyl iodide in place of ethyl iodide gives a mixture of *N*-substituted imidate and the *N,N*-disubstituted amide (Eq. 59) [85c].



$$C_6H_5\overset{\overset{O}{\|}}{C}-NH_2 \longrightarrow C_6H_5-\overset{\overset{NH}{\|}}{C}-OAg \xrightarrow{C_2H_5I} C_6H_5-\overset{\overset{NH}{\|}}{C}-OC_2H_5 \qquad (56)$$



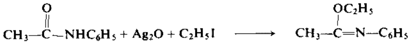
$$CH_3-\overset{\overset{NC_6H_5}{\|}}{C}-OAg + C_2H_5I \longrightarrow CH_3\overset{\overset{NC_6H_5}{\|}}{C}-OC_2H_5 \qquad (57)$$



$$CH_3-\overset{\overset{O}{\|}}{C}-NHC_6H_5 + Ag_2O + C_2H_5I \longrightarrow CH_3-\overset{\overset{NC_6H_5}{\|}}{C}-OC_2H_5 \qquad (58)$$

$$\xrightarrow[CH_3I]{Ag_2O} CH_3\overset{\overset{NC_6H_5}{\|}}{C}-OCH_3 + CH_3-\overset{\overset{O}{\|}}{C}-N\left\langle\begin{matrix}CH_3\\ C_6H_5\end{matrix}\right. \qquad (59)$$

### *2-13. Preparation of Ethyl* N*-Phenylacetimidate* [86a]

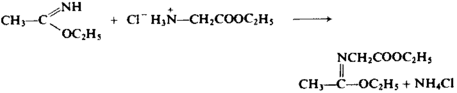


$$CH_3-\overset{\overset{O}{\|}}{C}-NHC_6H_5 + Ag_2O + C_2H_5I \longrightarrow CH_3-\overset{\overset{OC_2H_5}{|}}{C}=N-C_6H_5 \qquad (60)$$

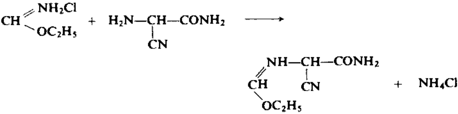
To a flask containing a hot solution of 47.0 gm (0.3 mole) of ethyl iodide and 13.5 gm (0.1 mole) of acetanilide is added 35 gm (0.15 mole) of dry silver oxide powder in small portions, causing a mild reaction. After the addition is complete the exothermic reaction continues on its own for $1\frac{1}{2}$ hr and then is refluxed for 1 hr. The product is extracted into ether, concentrated, filtered of unreacted acetanilide, and the residue fractionally distilled under reduced pressure to afford 9.0 gm (55.2%), b.p. 99–100°C (10 mm Hg).

## F. Reaction of Imidates To Give *N*-Substituted Imidates

Schmidt [87] earlier reported that amino acid esters react with imidates to give *N*-substituted imidates. The reaction has been shown to be of wide utility and the products are stable [88–90]. For example, 1 mole of ethyl aminoacetic acid hydrochloride reacts with ethyl acetimidate to give ethyl *N*-carboethoxymethylacetimidate [88] (Eq. 61). A similar reaction takes place with amino nitrites [91] and amino amides (Eq. 62) [92].



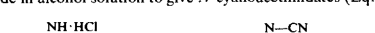
$$CH_3-C(=NH)OC_2H_5 + Cl^- H_3\overset{+}{N}-CH_2COOC_2H_5 \longrightarrow CH_3-C(=NCH_2COOC_2H_5)-OC_2H_5 + NH_4Cl \quad (61)$$



$$CH(=NH_2Cl)OC_2H_5 + H_2N-CH(CN)-CONH_2 \longrightarrow CH(=N-CH(CN)-CONH_2)OC_2H_5 + NH_4Cl \quad (62)$$

Thioimidates [93a, b] in most cases give imidazoles, but a few *N*-substituted thioimidates [37b] have been obtained by the above reaction. In addition, aminomalonamide also reacts to give imidazoles in place of the expected *N*-substituted imidate [94].

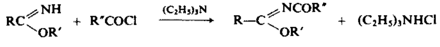
Recently it has been reported that acetimidate hydrochlorides react with cyanamide in alcohol solution to give *N*-cyanoacetimidates (Eq. 63) [69b].



$$R-\overset{NH\cdot HCl}{\overset{\|}{C}}-OR' + H_2N-CN \xrightarrow{R'OH} R-\overset{N-CN}{\overset{\|}{C}}-OR' + NH_4Cl \quad (63)$$

R = $CH_3$ and R′ = $C_2H_5$ or $CH_3$

The reaction fails when R becomes more complex than alkyl. Imidates also can be acylated with acyl chlorides to give acylimidates in 59–88% yields as shown in Eq. 64 and Table XII [95].



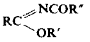
$$RC(=NH)OR' + R''COCl \xrightarrow{(C_2H_5)_3N} R-C(=NCOR'')OR' + (C_2H_5)_3NHCl \quad (64)$$

### 2-14. *General Procedure for the Preparation of Acylimidates* [95]

To a flask containing a stirred solution of 0.30 mole of an imidate and 0.33 mole of triethylamine in 300 ml of methylene chloride cooled to below 0°C is added dropwise over a period of ½ hr 0.30 mole of an acyl chloride in 50 ml of methylene chloride. The reaction mixture is stirred for about 20 hr at room temperature and the precipitated solid is filtered off. The solvent is

TABLE XII

ACYLIMIDATES



$$RC\begin{matrix}\nearrow NCOR'' \\ \searrow OR'\end{matrix}$$

| R = | R″ = | R′ = | Yield (%) | B.p., °C (mm Hg) | $n_D$ (°C) |
|---|---|---|---|---|---|
| Et | Et | *i*-Pr | 88.0 | 78–80 (15) | 1.4320 (29) |
| Et | Me | *i*-Pr | 73.8 | 63 (10) | 1.4295 (27) |
| Et | CH=CHPh | *i*-Pr | 83.1 | 121.5 (0.2) | 1.6215 (28) |
| Et | Ph | *i*-Pr | 59.0 | 99 (0.2) | 1.5140 (31) |
| Ph | Et | Me | 76.0 | 158 (22) | 1.5290 (29) |

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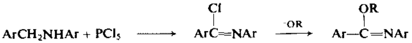
removed and the residue is redissolved in pentane to precipitate additional solid. The solvent is removed and the residue is fractionally distilled to give the acylimidates shown in Table XII.

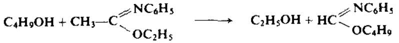
## 3. MISCELLANEOUS METHODS

(1) Preparation of *N*-phenylbenzimido chloride and reaction with alcoholic alkoxides to give imido esters [96].



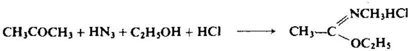
$$ArCH_2NHAr + PCl_5 \longrightarrow Ar\overset{\overset{\displaystyle Cl}{|}}{C}{=}NAr \xrightarrow{^-OR} Ar{-}\overset{\overset{\displaystyle OR}{|}}{C}{=}NAr \qquad (65)$$

(2) Preparation of imidates by transesterification with an alcohol of higher boiling point [97a,b]. For example [98]:



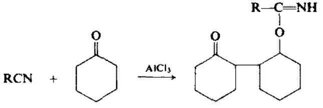
$$C_4H_9OH + CH_3{-}C\begin{matrix}\nearrow NC_6H_5 \\ \searrow OC_2H_5\end{matrix} \longrightarrow C_2H_5OH + HC\begin{matrix}\nearrow NC_6H_5 \\ \searrow OC_4H_9\end{matrix} \qquad (66)$$

(3) Reaction of ketones with hydrozoic acid in the presence of alcoholic hydrogen chloride [99].



$$CH_3COCH_3 + HN_3 + C_2H_5OH + HCl \longrightarrow CH_3{-}C\begin{matrix}\nearrow NCH_3HCl \\ \searrow OC_2H_5\end{matrix} \qquad (67)$$

(4) Reaction of nitriles with cyclohexanone in the presence of aluminum chloride to give imidates [100].

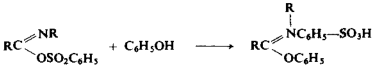


(68)

R = $CH_3$, $C_2H_5$, or $C_6H_5$

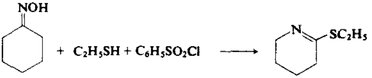
(5) Reaction of aldonitrones with methanolic potassium cyanide to give imidates [101, 102].

(6) Reaction of imidosulfonates with phenols [103].



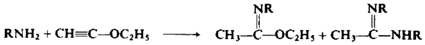
$$RC\begin{matrix}\nearrow NR\\ \searrow OSO_2C_6H_5\end{matrix} + C_6H_5OH \longrightarrow RC\begin{matrix}\overset{R}{|}\\ \nearrow NC_6H_5{-}SO_3H\\ \searrow OC_6H_5\end{matrix} \qquad (69)$$

(7) Reaction of cyclohexanone oxime with ethanethiol and benzenesulfonyl chloride [104].



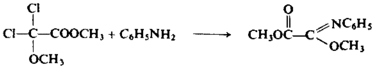
(70)

(8) Addition of primary amines to ethoxyacetylene in refluxing ethanol [105]. Secondary amines do not undergo this reaction [105].



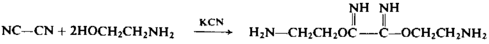
$$RNH_2 + CH{\equiv}C{-}OC_2H_5 \longrightarrow CH_3{-}\overset{\overset{NR}{\|}}{C}{-}OC_2H_5 + CH_3{-}\overset{\overset{NR}{\|}}{C}{-}NHR \qquad (71)$$

(9) Preparation of methyl *N*-phenylcarbomethoxyformimidate by the reaction of methyl methoxydichloroacetate on aniline in boiling xylene [106, 107].



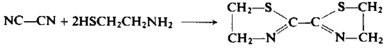
$$Cl{-}\underset{\underset{OCH_3}{|}}{\overset{\overset{Cl}{|}}{C}}{-}COOCH_3 + C_6H_5NH_2 \longrightarrow CH_3O\overset{\overset{O}{\|}}{C}{-}C\begin{matrix}\nearrow NC_6H_5\\ \searrow OCH_3\end{matrix} \qquad (72)$$

(10) Reaction of cyanogen with ethanolamine in dilute potassium cyanide solution [108].



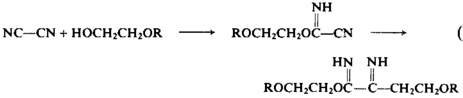
$$NC{-}CN + 2HOCH_2CH_2NH_2 \xrightarrow{KCN} H_2N{-}CH_2CH_2O\overset{\overset{NH}{\|}}{C}{-}\overset{\overset{NH}{\|}}{C}{-}OCH_2CH_2NH_2 \tag{73}$$

(11) Reaction of cyanogen with 2-mercaptoethylamine in aqueous solution [109].



(74)

(12) Reaction of cyanogen with methyl Cellosolve [10].

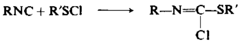


$$NC{-}CN + HOCH_2CH_2OR \longrightarrow ROCH_2CH_2O\overset{\overset{NH}{\|}}{C}{-}CN \longrightarrow ROCH_2CH_2O\overset{\overset{HN}{\|}}{C}{-}\overset{\overset{NH}{\|}}{C}{-}CH_2CH_2OR \tag{75}$$

(13) Reaction of cyanogen and thiols using basic catalysts to give oxaldithioimidates [111].

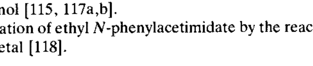
(14) Reaction of $\alpha$-chloro and $\alpha,\alpha$-dichloro nitriles with alcohol in sodium cyanide solution at pH 9.5 at 80°C to afford imidates [112].

(15) Reaction of isocyanides with sulfenyl chlorides to give chlorothioformimidates [113].



$$RNC + R'SCl \longrightarrow R{-}N{=}\underset{\underset{Cl}{|}}{C}{-}SR' \tag{76}$$

(16) Preparation of cyclic imidates by the dehydration of *N*-2- and *N*-(3-hydroxyalkyl)amides or dehydrohalogenation of *N*-(3-haloalkyl)-amides [114a,b, 115].



(77)

(17) Preparation of cyclic imidates by the reaction of acyclic imidic esters or their hydrochlorides with 2-aminoethanol [115, 116a,b] or with 3-aminopropanol [115, 117a,b].

(18) Preparation of ethyl *N*-phenylacetimidate by the reaction of aniline and ketene acetal [118].

(19) Preparation of ethyl *N*-phenylpropionimidate from aniline and 1-ethoxypropyne [119].

(20) Preparation of alkyl *N*-cyanoimidates [120].

(21) Preparation of thioimidate *N*-oxides [21].

(22) Preparation of the thioimidate by reaction of thiophenol with diphenylketene *N*(-*p*-bromophenyl)imine [122].

(23) Formation of imidates from the $\mu_3$-NPh ligands of $Fe_3(\mu_3NPh)_2(CO)_9$ [123].

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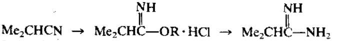

$Me_2CHCN \rightarrow Me_2CH\overset{NH}{\overset{\|}{C}}-OR\cdot HCl \rightarrow Me_2CH\overset{NH}{\overset{\|}{C}}-NH_2$

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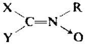
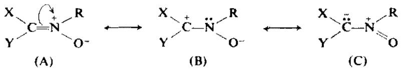
## 1. INTRODUCTION

Azomethine *N*-oxides or nitrones have the following characteristic functional group:



The name "nitrone" is obtained from the contraction of the name "nitrogen ketone" [1]. The nitrone functional group is capable of resonance, as shown in Eq. 1 [2]. Structure (A) appears to be the most important contributing form.



(1)

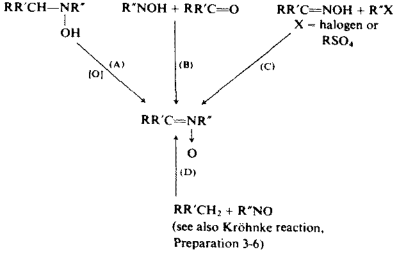
When the nitrone group is part of an aromatic system (pyridine and quinoline *N*-oxides) there is considerable delocalization of the positive charge and these are therefore not considered to have the same nitrone group reactivity [3a]. In addition, if X or Y = oxygen as part of a ring system (isoxazoline-2-oxide and furoxans), a similar reduction in properties also occurs. However, if X or Y = aryl, alkyl, or ketone there is no reduction in properties. When X or Y are electron-withdrawing groups the electrophilic properties of the groups are enhanced. For example, $\alpha$-benzoyl-*N*-phenylnitrone undergoes 1,3-cycloaddition 110 times faster than $\alpha$-*N*-diphenylnitrone [4].

The nitrone functional group activates adjacent CH, $CH_2$, or $CH_3$ groups for proton removal, oxidation, addition of organometallics or hydrocyanic acid, and reduction reactions by complex metal hydrides [5].

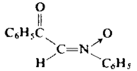
Substituted nitrones exhibit cis-trans isomerism [6a–e] and the cis forms are readily converted to the trans forms by heating [6d]. The structural assignments are based on dipole moment studies, IR, UV, and NMR analysis [6a–e].

*Chemical Abstracts* nomenclature for nitrones uses the prefix $\alpha$ for groups attached to the carbon atom and N for groups attached to the

SCHEME 1
Methods of Preparation of Nitrones



nitrogen. For example,

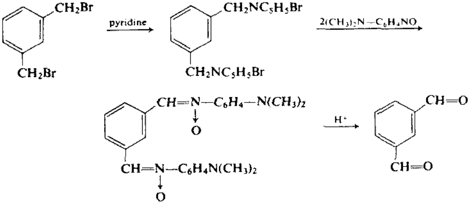


α-Benzoyl-*N*-phenylnitrone

Nitrones are best prepared by the oxidation of N,N-disubstituted hydroxylamines, by the reaction of N-substituted hydroxylamines with ketones, and by the reaction of aromatic nitroso compounds with activated methyl or methylene groups. The alkylation of oximes gives mixtures of the oxime *O*-ethers and nitrones and is therefore of limited use.

Each of the above methods is described by equations in Scheme 1 and several preparative examples are provided in Table I.

The Kröhnke reaction [23] has been used to prepare a wide variety of carboxyl compounds by the hydrolysis [24] of the appropriate nitrone. Typical of these carbonyl compounds are aldehydes, glyoxals, α,β-unsaturated aldehydes, dialdehydes, ketones, α-ketocarboxylic acids, and carboxylic acids [24–26]. A typical example is shown in Eq. 2.



(2)

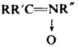
Sensitive aliphatic aldehydes [27–31] and aromatic mono- [30, 32, 33], di- [34], and tricarboxaldehydes [34] have also been prepared via nitrones (Eq. 3). Nitrone formation and hydrolysis is particularly helpful in preparing steroid aldehydes [35–45].

$$RR'C{=}\underset{\underset{O}{\downarrow}}{N}{-}R'' + H_2O \longrightarrow R{-}\underset{\underset{O}{\|}}{C}{-}R' + R''NHOH \qquad (3)$$

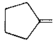
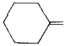
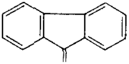
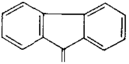
R, R′, R″ = alkyl or aryl (ketones)
R or R′ may = H (aldehydes)

# TABLE I

### THE PREPARATION OF NITRONES BY THE METHODS SHOWN IN SCHEME I



$$RR'C{=}\overset{\displaystyle NR''}{\underset{\displaystyle O}{\downarrow}}$$

| R = | R′ = | R″ = | Method (see Scheme I) | Yield (%) | B.p., °C (mm Hg) or m.p., °C | Ref. |
|---|---|---|---|---|---|---|
| $CH_3$ | H | $C_6H_5$ | A | — | 58–60 | 7, 8 |
| $n$-$C_3H_7$ | H | $C_6H_5$ | A | 74–80 | 75 | 8 |
| $C_6H_5$ | H | $CH_3$ | A | — | 84 | 9 |
| $C_6H_5$ | H | $C_6H_5$ | A | 60 | 112 | 8, 10, 11 |
| $C_6H_5$ | H | $C_6H_5CH_2$ | A | 90 | 81.5–83.5 | 9, 12, 13 |
| $n$-$C_3H_7$ | H | $C_6H_5$ | B | 21–80 | 71–74 | 7, 8 |
| $C_6H_5$ | H | $CH_3$ | B | — | 81–82 | 14 |
| $C_6H_5$ | H | $C_6H_5$ | B | 90 | 112–114 | 10, 15, 16 |
| $C_6H_5$ | H | $C_6H_5CH{=}CH$ | B | — | 73 | 11 |
| $C_6H_5$ | H | $(C_6H_5)_2CH$ | B | 80 | 159–160 | 11 |
| $C_6H_5$ | $C_6H_5$ | $C_6H_5CH_2$ | B | 65 | 119–120 | 9, 12 |
| $C_6H_5$ | $C_6H_5$ | $CH_3$ | B | — | 103 | 17 |
| $C_6H_5$ | $CH_3$ | $CH_3$ | B | — | 115 | 17 |
| $C_6H_5$ | $CH_3$ | $CH_3$ | B | — | 77 (2) | 17 |
|  |  | $CH_3$ | B | 61 | 85 (2) | 17 |
|  |  | $CH_3$ | B | — | 96 (1) | 17 |
| $n$-$C_3H_7$ | H | $C_6H_5CH_2$ | C | — | 135–136 (26) | 18 |
| $n$-$C_7H_{15}$ | H | $C_6H_5CH_2$ | C | 77 | 88–90 | 18 |
| $n$-$C_8H_{17}$ | H | $C_6H_5CH_2$ | C | — | 91.5–92.5 | 18 |
| $C_6H_5$ | H | $(C_6H_5)_2CH$ | C | 6–22 | 157–161 | 19 |
| $C_6H_5$ | $C_6H_5$ | $CH_3$ | C | 43 | 102–103 | 19 |
| $C_6H_5$ | $C_6H_5$ | $C_6H_5CH_2$ | C | 17–22 | 119–122 | 19 |
| $C_6H_5$ | $C_6H_5$ | $(C_6H_5)_2CH$ | C | 31 | 162–166 | 12 |
| $C_6H_5$ | H | $C_6H_5$ | D | 25 | 112–113 | 20 |
| $C_6H_5$ | $C_6H_5$ | $C_6H_5$ | D | 60–68 | 223–226 | 21 |
|  |  | $C_6H_5$ | D | 88–96 | 194–197 | 21 |
|  |  | $(CH_3)_2NC_6H_4$ | D | — | 224d | 22 |

The nitrone group has found particular use in undergoing 1,3-cycloaddition reactions [3, 5] between methylene phosphorones [46], Michael olefins [47], alkenes [5], enamines [48], ynamines [49], enynes [50], sulfinylamines [51], acetylenic carboxylic esters [52], ketene acetals [53], isocyanates [8, 54–56], and recently with intermediary sulfenes [57].

Nitrones are also useful industrially in such areas as cross-linking agents [58], as light-sensitive compounds for printing plates [59], in pharmacological studies [60a–c], for the preparation of novel polymers [61a], for charge-transfer complexes [61b], as seed protectants [61c], as antifungal agents [61d], for autooxidation and stabilization of undoped and doped polyacetylenes [61e], for antioxidant activity in polymers such as polypropylene [61f], as spin trapping reagents [61g], and as antimicrobiol agents [61h].

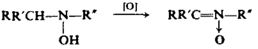
Aliphatic nitrones are in general more unstable than aromatic and alicyclic nitrones, particularly in the presence of water or even alcohol [62a–f]. The only crystalline aliphatic nitrone known is that derived from cyclohexylhydroxylamine [63]. Recently stable aliphatic nitrones have been reported with a cyano group on the carbon attached to the nitrone nitrogen [64].

The chemistry of nitrones was reviewed in 1938 [6b], 1964 [5], 1965 [3a], 1984 [3b], and 1985 [3c].

The use of nitrones in organic synthesis is developing rapidly [3d–f] and functionalized nitrones are one example.

## 2. OXIDATION REACTIONS

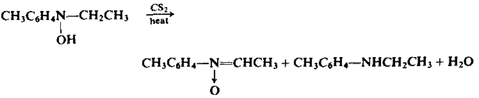
*N,N*-Disubstituted hydroxylamines can be oxidized to give cyclic and acyclic nitrones. The oxidizing agents usually employed are molecular oxygen [8a,b, 65], yellow mercuric oxide [55], "active" lead oxide [66], lead tetracetate [67], potassium ferricyanide [7, 8], potassium permanganate [8], cupric acetate [68], *t*-butyl hydroperoxide [69], hydrogen peroxide [10a], chromic acid [5], *N*-bromosuccinimide [8b], diacetoxyiodobenzene [8b], iodine [8b], and ceric ammonium nitrate [8b]. Base is required with $\mathrm{NBS(PhIIOAc)_2}$ and $I_2$ oxidants. This oxidation method is only applicable when at least one of the carbon atoms $\alpha$ to the nitrogen atom carries a hydrogen atom, as shown in Eq. 4. More recently, nitrones have been prepared by the electrochemical oxidation of *N*-hydroxy secondary amines, using halide ions as mediators [8c].



$$\mathrm{RR'CH{-}\underset{\displaystyle OH}{\underset{|}{N}}{-}R''} \xrightarrow{[O]} \mathrm{RR'C{=}\underset{\displaystyle O}{\underset{\downarrow}{N}}{-}R''} \qquad (4)$$

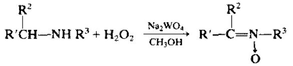
Recently azomethines have been oxidized to nitrones by hydrogen peroxide [62d] and peracetic acid [21].

In the absence of oxidizing agents and catalysts, hydroxylamines undergo a disproportionation to the nitrone and amine (Eq. 5) [7].



$$CH_3C_6H_4\underset{\underset{\text{OH}}{|}}{N}{-}CH_2CH_3 \xrightarrow[\text{heat}]{CS_2} CH_3C_6H_4{-}\underset{\underset{O}{\downarrow}}{N}{=}CHCH_3 + CH_3C_6H_4{-}NHCH_2CH_3 + H_2O \quad (5)$$

The tungstate catalyzed oxidation of secondary amines, using hydrogen peroxide, gives nitrones in good yields [10b], as seen in Eq. 6.



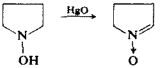
$$R'\overset{\overset{R^2}{|}}{C}H{-}NH\,R^3 + H_2O_2 \xrightarrow[CH_3OH]{Na_2WO_4} R'{-}\overset{\overset{R^2}{|}}{C}{=}\underset{\underset{O}{\downarrow}}{N}{-}R^3 \quad (6)$$

where

(1) $R' = nPr$, $R^2 = H$, $R^3 = n\text{Bu}$ Yield: 89%
(2) $R' = R^2 = CH_3$ $R^3 = i\text{Pr}$ Yield: 74%
(3) $R' = Ph$, $R^2 = H$, $R^3 = CH_2Ph$ Yield: 85%

4 mole % of $Na_2WO_4 \cdot 2H_2O$ and 3 equiv. of $H_2O_2$ were used at 0°C for 3 hrs.

### 2-1. *Preparation of Δ′-Pyrroline* N-*Oxide* [55]

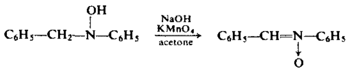


(7)

To a stirred solution of 5.0 gm (0.058 mole) of *N*-hydroxypyrrolidine in 150 ml of dry chloroform is added all at once 24.9 gm (0.115 mole) of yellow mercuric oxide. The reaction is exothermic and the mercuric oxide changes color first to green then to gray-black. After 2 hr stirring another 6.5 gm (0.03 mole) of yellow mercuric oxide is added and stirring is continued for an additional 2 hr. The reaction mixture is filtered, the solids washed with chloroform, and the filtrate concentrated under reduced pressure at 40°C to give a yellow-brown oil. The oil is dried under reduced pressure for 86 hr over $P_2O_5$ and distilled to afford 3.72 gm (72%) of a yellow oil, b.p. 65°C (0.07 mm Hg). Redistillation affords 3.02 gm (61%)

of a colorless oil, b.p. 57.5°C (0.04 mm Hg) (picrate obtained in ether or alcohol solution, m.p. 120°C).

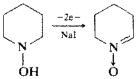
### 2-2. *Preparation of α,N-Diphenylnitrone* [10]



$$C_6H_5{-}CH_2{-}\overset{OH}{\overset{|}{N}}{-}C_6H_5 \xrightarrow[\text{acetone}]{\text{NaOH},\ \text{KMnO}_4} C_6H_5{-}CH{=}\underset{O}{\underset{\downarrow}{N}}{-}C_6H_5 \qquad (8)$$

To an ice-cooled flask containing 20.0 gm (0.10 mole) of benzylphenylhydroxylamine dissolved in 100 ml of acetone and 10 ml of 2 *N* sodium hydroxide solution is added dropwise a solution of 11.0 gm (0.70 mole) of potassium permanganate in 200 ml of acetone. The addition is continued until the permanganate color remains, the reaction is filtered of manganese dioxide, neutralized with 2 *N* hydrochloric acid, and then calcium chloride is added. Two layers appear and the acetone layer is separated and dried. The acetone is concentrated under reduced pressure at room temperature to afford a crude solid which is recrystallized from alcohol or benzene–petroleum ether to afford 11.8 gm (60%), m.p. 112°C.

### 2-3. *The Electrochemical Oxidation of* N-*Hydroxypiperidine to the Nitrone* [8c]



(9)

To an undivided cell equipped with a platinum anode and a carbon cathode is placed a solution of 35 mmol *N*-hydroxypiperidine and 1 mmol sodium iodine in 30 ml methanol. A constant current of 0.2 ampere is passed through the cell with external cooling by ice-water. After 2.5 F/mole of electricity was passed, the solvent is removed under reduced pressure, and the resulting residue is chromatographed on a silica gel column using a solvent (1:10 methanol: ethylacetate) to afford the nitrone in 85% yield. (The yield of the nitrone was determined by NMR [8d], using ethyl orthoformate as a standard compound.)

4-Membered cyclic nitrones have been reported to be prepared by the oxidation of the *N*-hydroxyazetidine with lead oxide [8e].

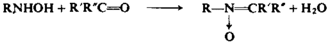
The use of *m*-chloroperoxybenzoic acid has been used to oxidize $PhCH_2NHC_6H_4R_{(p)}$ (where R = H, Cl, $CH_3$) to the nitrone [8f] and other tertiary amines [8g].

## 3. CONDENSATION REACTIONS

The main condensation reactions used to prepare nitrones are (A) the reaction of hydroxylamines with aldehydes and ketones, (B) the reaction of aromatic nitroso compounds with activated methyl and methylenes, and (C) the alkylation of oximes. Methods A and B give good yields and relatively pure nitrones, without any oxime ether impurities, as are normally found in method C.

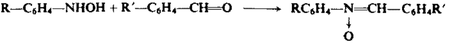
### A. Reaction of *N*-Substituted Hydroxylamines with Aldehydes and Ketones

The reaction of *N*-substituted hydroxylamines with aldehydes and ketones proceeds best when R = alkyl or aryl and R′ and R″ = small size groups (Eq. 8). If R′ and R″ are large, then the resulting steric effects afford low yields of nitrones. For example, *N*-diphenylmethylhydroxylamine or *N*-cinnamyl-hydroxylamine readily react with benzaldehyde to give the nitrone. *N*-Triphenylmethylhydroxylamine does not afford nitrone upon reaction with benzophenone [11]. This method is of general application and is useful to prepare a wide variety of nitrones. In most cases the reaction proceeds more readily with aldehydes rather than with ketones.



$$\mathrm{RNHOH + R'R''C{=}O \longrightarrow R{-}\underset{\substack{\downarrow\\ O}}{N}{=}CR'R'' + H_2O} \qquad (10)$$

### *3-1. General Procedure for the Preparation of Phenylnitrones* [15a]



$$\mathrm{R{-}C_6H_4{-}NHOH + R'{-}C_6H_4{-}CH{=}O \longrightarrow RC_6H_4{-}\underset{\substack{\downarrow\\ O}}{N}{=}CH{-}C_6H_4R'} \qquad (11)$$

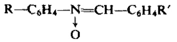
Equimolar amounts of the appropriate phenylhydroxylamine and benzaldehyde are dissolved in the minimum amount of ethanol. The mixtures are allowed to stand at room temperature overnight, filtered, and then recrystallized from ethanol to afford an 80–95% yield of the nitrones shown in Table II.

Recently, a series of these compounds has been prepared by this method and claimed for relief of inflammation and associated pain/fever by their topical administration [15c].

The preparation of *N*-methylphenylnitrones is reported to give 98% yields when *N*-methylhydroxylamine sulfite is reacted with benzaldehyde

TABLE II

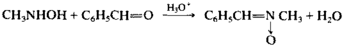
PREPARATION OF NITRONES USING PROCEDURE 3-1



$$R{-}C_6H_4{-}\underset{O}{\underset{\downarrow}{N}}{=}CH{-}C_6H_4R'$$

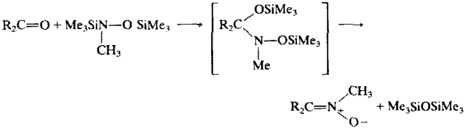
| R = | R′ = | M.p. (°C) |
|---|---|---|
| H | H | 114 |
| 2-OH | H | 118 |
| 3-OH | H | 230 |
| 4-OH | H | 212 |
| 4-$OCH_3$ | H | 116 |
| 3-$OCH_3$<br>4-OH | H | 215 |
| 2-$NO_2$ | H | 137 |
| 3-$NO_2$ | H | 154 |
| 4-$NO_2$ | H | 189 |
| 4-OH | 2-$CH_3$ | 187 |
| H | 4-$CH_3$ | 123 |
| H | 4-Cl | 181 |

at 65°C using aqueous sodium hydroxide [15b]. The pH of the aqueous phase is not allowed to exceed 6.



$$CH_3NHOH + C_6H_5CH{=}O \xrightarrow{H_3O^+} C_6H_5CH{=}\underset{O}{\underset{\downarrow}{N}}\,CH_3 + H_2O \tag{12}$$

Recently, the reaction of *N*-methyl-*N*,*O*-bis (trimethylsilyl) hydroxylamine with aldehyde and ketone gives good yields of *N*-methylnitrones under very mild conditions [15f].

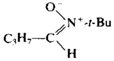
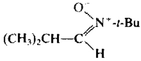
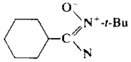
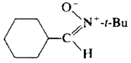
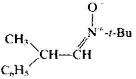


$$R_2C{=}O + Me_3Si\underset{CH_3}{\underset{|}{N}}{-}O\,SiMe_3 \longrightarrow \left[R_2C\begin{matrix}OSiMe_3\\ \underset{Me}{\underset{|}{N}}{-}OSiMe_3\end{matrix}\right] \longrightarrow R_2C{=}\overset{+}{N}\begin{matrix}CH_3\\ O^-\end{matrix} + Me_3SiOSiMe_3 \tag{13}$$

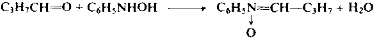
The reaction of *N*-*tert*-butylhydroxylamine with the appropriate aliphatic aldehydes in methylene chloride in the presence of suspended sodium sulfate, by the procedure of Torssele and Zeuthen [15d], gives good yields (70–90%) of the nitrone [15e], as described in Table III.

TABLE III

PREPARATION OF NITRONES BY THE REACTION OF ALDEHYDES WITH *N-tert*-BUTYLHYDROXYLAMINE [15e]

| Aldehyde | Nitrone | Physical property | % Yield |
|---|---|---|---|
| *n*-Butyraldehyde |  | b.p. 50–53°C<br>(0.45 mm Hg) | 93 |
| Isobutyraldehyde |  | b.p. 55–58°C<br>(0.9 mm Hg) | 72 |
| Cyclohexane Carboxaldehyde |  | m.p. 59–61°C | 80 |
| 3-Cyclohexane Carboxaldehyde |  | m.p. 35–37°C | 59 |
| 2-Phenylpropionaldehyde |  | m.p. 53–56°C | 88 |

### 3-2. *Preparation of α-Propyl-N-phenylnitrone* [8]

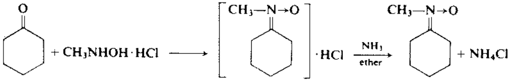
 (14)

$$C_3H_7CH{=}O + C_6H_5NHOH \longrightarrow \underset{\downarrow \atop O}{C_6H_5N}{=}CH{-}C_3H_7 + H_2O \qquad (14)$$

To a flask containing a solution of 55 gm (0.51 mole) of phenylhydroxylamine in 400 ml of dry ether at 0°C and 20 gm (0.18 mole) of calcium chloride is added dropwise with stirring 36 gm (0.50 mole) of *n*-butyraldehyde over a 1 hr period. The reaction mixture is filtered from the calcium chloride hydrate and the ether concentrated under reduced pressure to afford an oily residue. The residue is shaken with 400 ml of petroleum ether, filtered, and the clear solution cooled at −15°C for 24 hr. Yellow crystals separate which upon two recrystallizations from ligroin afford 64.8 gm (80%) [7], m.p. 71–74°C.

Cyclic ketones such as cyclopentanone and cyclohexanone react with methylhydroxylamine hydrochloride to give the hydrochloride salt of the nitrone. The free nitrone is obtained by passing ammonia through an ether solution, filtering the ammonium chloride, and concentrating the ether.

### *3-3. Preparation of α-Cyclohexyl-N-methylnitrone* [62a]

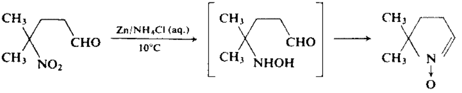


(15)

An anhydrous mixture of 4.2 gm (0.05 mole) of methylhydroxylamine hydrochloride and 15 gm (0.153 mole) of cyclohexanone is warmed for 3 hr at 70°C, cooled, rapidly filtered at −10°C, and the solids dried under reduced pressure over $P_2O_5$ to give 5.0 gm (61%) of the hydrochloride salt, m.p. 138°C. This salt is added to 15 ml of dry ether and then ammonia slowly added over a 2-hr period while stirring. The resulting ammonium chloride is filtered and the ether concentrated under reduced pressure to afford 3.2 gm (50%) of the free nitrone, b.p. 96°C (1 mm Hg), $n_D^{20}$ 1.5014, $d_D^{20}$ 1.0526.

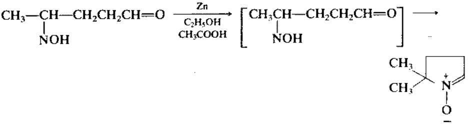
The hydroxylamino function can also be generated *in situ* by the zinc dust reduction of a nitro compound [70]. On the other hand, the aldehyde or ketone can be liberated *in situ* from the bisulfite addition compound [71] or the acetal [62e].

Cyclic nitrones can be formed by the controlled reduction of α-nitroaldehydes or α-nitro ketones (Eq. 16) [72a]. The free aldehyde group can be protected before the zinc reduction step by acetylation with ethylene glycol and then freed by mild acid treatment.



(16)

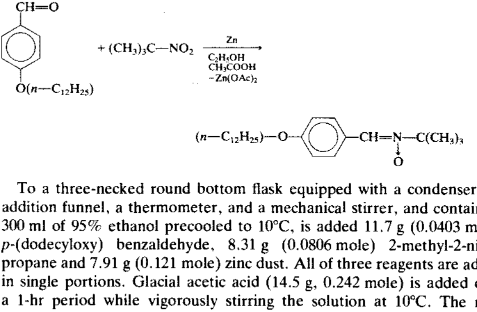
### *3-4. Preparation of 5,5-Dimethyl-1-pyrroline N-Oxide* [72b]



(17)

To a three-necked round bottom flask equipped with a condenser, addition funnel, thermometer, and mechanical stirrer and containing 300 ml. 95% ethanol precooled to 2°C is added, all at once, 14.5 g (0.1 mole) 4-methyl-4-nitropentanol, and 13.1 g (1.2 mole) zinc dust. With rapid agitation, the glacial acetic acid (24.0 g, 0.4 mole) is added dropwise over a 1-hr period while maintaining the reaction temperature below 15°C. The mixture is stirred vigorously for 2 hr and then stored in the refrigerator for 2 days, at approximately 1°C. Then the zinc acetate is filtered and rinsed with 100 ml of ethanol. The combined ethanol factions are rotoevaporated to give the crude nitrone. The crude nitrone is dissolved in a 200 ml portion of dichloromethane and the latter washed two times with saturated sodium bicarbonate solution. The organic layer is dried over sodium sulfate and the solvent rotoevaporated, to give 10.7 (94% yield) of the crude nitrone. The product was purified by double distillation (b.p. 53°C, 0.1 Torr), to give 6.8 g (60%) of the pure nitrone as a white hygroscopic solid. The $H^1$ NMR (400 MH, $CDCl_3$, $Me_4Si$) is 6.80 (*t*, 2H, methylene bound to quaternary C, $J = 7.2$ Hg), 1.43 (*s*, 6H, methyl), $C^{13}$NMr (100 $MH_2$, $CDCl_3$, $Me_4$ Si) $\delta = 132.4$ (Vinyl), 73.5 (quaternary), 34.1 (Allyl), 25.3 (methylene bound to quaternary C), 24.4 (methyls).

*3-5. **Preparation of (Dodecyloxy)phenyl-tert-butylnitrone*** [72c]



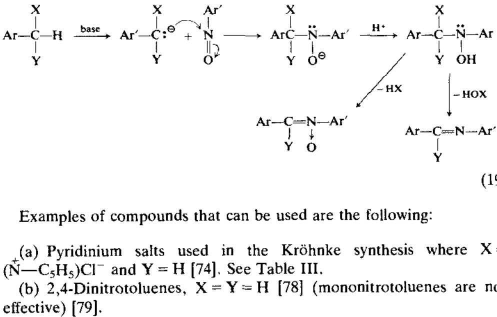
(18)

To a three-necked round bottom flask equipped with a condenser, an addition funnel, a thermometer, and a mechanical stirrer, and containing 300 ml of 95% ethanol precooled to 10°C, is added 11.7 g (0.0403 mole) *p*-(dodecyloxy) benzaldehyde, 8.31 g (0.0806 mole) 2-methyl-2-nitropropane and 7.91 g (0.121 mole) zinc dust. All of three reagents are added in single portions. Glacial acetic acid (14.5 g, 0.242 mole) is added over a 1-hr period while vigorously stirring the solution at 10°C. The mixture is stirred for an additional 2 hr and then stored in the refrigerator for 48 hr at approximately 6°C. The sample is then filtered to remove the zinc acetate and the solvent evaporated. The solid nitrone is taken up in 150 ml of ether and washed once with 100 ml water. The solid zinc acetate is also rinsed once with ether. The combined ether portions are dried and then the ether removed to yield 12.9 g (88.4% yield) crude nitrone, m.p. 58–63°C.

Recrystallization from acetone/water gave 11.1 g (76% yield) of fluffy white crystals, m.p. 62–64°C (lit. 61 g, m.p. 60–62°C). The NMR ($CDCl_3$, $Me_4Si$) indicated $\delta$ 8.24 ($d$, $J = 9H_z$, 2H), 7.42 ($s$, 1H) 6.88 ($d$, $J = 9H_z$, 2H) 3.98 ($t$, J 6.5$H_z$, 2H) 1.57 ($s$, 9H), 1.40–0.67 ($m$, 2H); IR ($cm^{-1}$)2900, 2830, 1585, 1460.

### *B. Nitrones via Condensation Reaction of Aromatic Nitroso Compounds with Activated Methyl or Methylene Groups*

Aromatic nitroso compounds readily react with activated methylene or methyl groups to give new nitroso compounds. The reaction is usually catalyzed by small amounts of base (sodium carbonate, pyridine, or piperidine) to give either the anil (1,2-elimination) or nitrone (1,3-elimination), as shown in Eq. (13) (73–77]. If X = H, then the elimination to the nitrone is an oxidation, and the excess of nitroso compound acts as the oxidizing agent.



(19)

Examples of compounds that can be used are the following:

(a) Pyridinium salts used in the Kröhnke synthesis where X = $(\overset{+}{N}—C_5H_5)Cl^-$ and Y = H [74]. See Table III.

(b) 2,4-Dinitrotoluenes, X = Y = H [78] (mononitrotoluenes are not effective) [79].

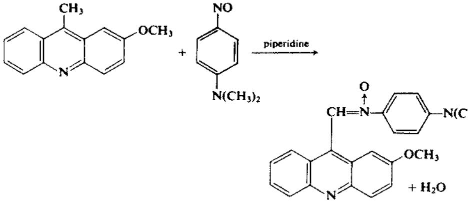
(c) Lepidine *N*-oxide [80], quinaldine *N*-oxide [81, 82], and 2- and 4-picolines [72, 74] are also active in reacting to give nitrones. In addition the following others are effective: methylacridine [83, 84], 2-methylchromone [85], 2-methylthiochromone [86], 5-methyl-1, 2-dithiol-3-thiones [87].

(d) Benzyl chloride [88], benzyl cyanide [88], α-chloro-α-cyanotoluene [89], and (*p*-cyclohexylphenyl)acetonitrile [90].

(e) Fluorene [91] and similar compounds [92–95].

Several other compounds react with aromatic nitroso compounds, but the generality of their reaction has not been established and they are listed in the Miscellaneous Methods section of this chapter.

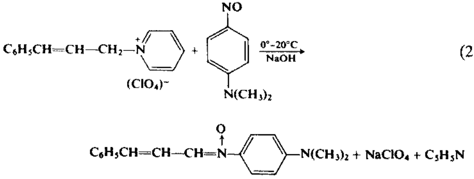
### 3-6. *Preparation of α-(2-Methoxy-9-acridyl)-*N*-(4-dimethylaminophenyl)-nitrone* [75]



(20)

To a flask is added 8.0 gm (0.036 mole) of 2-methoxy-9-methylacridine, 10.8 gm (0.072 mole) of *p*-nitrosodimethylaniline, and 6 drops of piperidine. The reaction is heated on an oil bath to 95°C and when the initial exothermic reaction subsides the reaction mixture is heated at 120°C for $\frac{1}{2}$ hr. After this time, the reaction mixture is cooled, 10 ml of ethanol, and 150 ml of ether added, filtered, and recrystallized from ethanol to afford 10.8 gm (82%) of long, yellow rectangular plates, m.p. 225–227°C (dec).

### 3-7. *Preparation of α-Styryl-*N*-p-dimethylaminophenylnitrone (Kröhnke Reaction)* [96a]



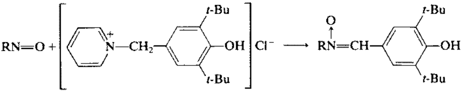
(21)

(*a*) *Cinnamyl pyridinium perchlorate.* To a stirred solution of 6.6 gm (0.034 mole) of cinnamylbromide in 6 ml of benzene at 20°C is added

2.9 gm (0.037 mole) of pyridine. After 2–3 hr the solid is filtered, boiled with benzene, and the remaining solid dissolved in hot water. Cinnamylpyridinium perchlorate is precipitated as an oil with 16 ml of 2 *N* perchloric acid, which on standing crystallizes. The product is purified by recrystallization from alcohol-ether to afford white platelets, m.p. 73–74°C. In many other cases of the Kröhnke reaction the pyridium halides may be used directly in the next step. (See Table IV). *Caution*: Percluoric acids and their salts, especially if dry, can be shock sensitive and should be handled with great care.

(*b*) *Nitrone preparation.* To a solution of 2.95 gm (0.01 mole) of cinnamyl-pyridinium perchlorate in 40 ml of 80% aqueous ethanol is added 1.65 gm (0.011 mole) of *p*-nitrosodimethylaniline in 30 ml of alcohol and 10 ml of 1 *N* NaOH. The reaction is stirred for 16 hr at 0–20°C and filtered to afford 1.87 gm (70%), m.p. 180°C (recrystallized from *n*-propanol).

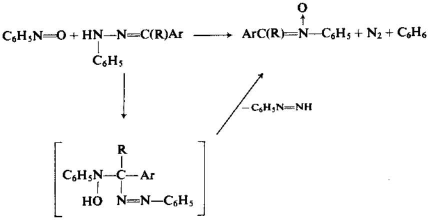
Recently, a series of rubber antioxidants have been prepared by the reaction of nitroso compounds and 3,5-di-*t*-butyl-4-hydroxybenzylpyridinium chloride as shown in Eq. 22 [96b].



(22)

Other examples of the Kröhnke reaction are shown in Table IV.

Recently Landolt and co-workers [97] reported a new synthesis of nitrones involving the reaction of readily available phenylhydrazones of aromatic aldehydes and ketones with nitrosobenzene as shown in Eq. [23].

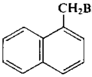
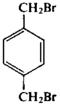
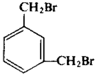
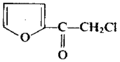


(23)

R = alkyl or aryl

## TABLE IV

### PREPARATION OF NITRONES VIA THE KRÖHNKE REACTION: CONDENSATION OF AROMATIC HALOMETHYL PYRIDINIUM SALTS WITH *p*-DIMETHYLAMINONITROSOBENZENE

| Halomethyl Compound | Yield (%) | M.p. (°C) | Ref. |
|---|---|---|---|
| $RC_6H_4CH_2X$,[c]<br>R = | | | |
| H | 75 | 144 | *a* |
| *p*-$NO_2$ | 100 | 206 | *a* |
| *m*-$NO_2$ | 100 | 168.5 | *a* |
| *m*-Cl | 61 | 118 | *a* |
| *p*-Cl | 73 | 178 | *a* |
| *p*-Br | 75 | 193 | *a* |
| *p*-$CH_3O$ | 52 | 146–147 | *a* |
| $C_6H_5—CH=CH—CH_2Br$ | 70 | 180 | *a* |
|  | 60 | 127–129 | *a* |
|  | 77 | >225 (dec.) | *a* |
|  | 34 | 193 | *a* |
|  | 61 | 123–125 | *b* |

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[a] F. Kröhnke, *Ber.* **71**, 2583 (1938). [b] F. Kipnis and J. Ornfelt, *J. Amer. Chem. Soc.* **70**, 3948 (1948). [c] X = Br in all cases except for *m*-$Cl—C_6H_4—CH_2Cl$.

TABLE V

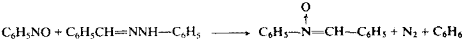
Reaction of Nitrosobenzene with Phenylhydrazones[a]

| Phenylhydrazone of aldehyde or ketone | Mole ratio of $C_6H_5NO$/phenylhydrazone | Yield (%) | M.p. (°C) |
|---|---|---|---|
| $C_6H_5$—CH═O | 1:1 | 65 | 112–114 |
| $C_6H_5$—CH═O | 2:1 | 100 | 112–114 |
| *p*-$NO_2$—$C_6H_4$—CH═O | 1:1 | 63 | 187–188 |
| *m*-$NO_2$—$C_6H_4$—CH═O | 1:1 | 63 | 149–150 |
| Cl—Cl—$C_6H_4$—CH═O | 1:1 | 38 | 153–154 |
| Fluorenone | 2:1 | 49 | 192–193 |

[a] Data from D. W. Berry, R. W. Bryant, J. K. Smith, and R. G. Landolt, *J. Org. Chem.* **35**, 845 (1970).

As seen in Table V, an excess of nitrobenzene tends to give higher yields. Little is known about the generality of this reaction and the possibility whether it can be applied to a large-scale preparation. The preparation of α, *N*-diphenylnitrone by the procedure of Eq. [23] is given only for information.

### 3-8. *Preparation of α,*N*-Diphenylnitrone* [97]

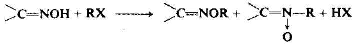


$$C_6H_5NO + C_6H_5CH{=}NNH{-}C_6H_5 \longrightarrow C_6H_5{-}\overset{\overset{\displaystyle O}{\uparrow}}{N}{=}CH{-}C_6H_5 + N_2 + C_6H_6 \quad (24)$$

To a three-necked flask equipped with a magnetic stirrer, pressure-equalizing dropping funnel, and drying tube-protected condenser is added 0.196 gm (1.0 mole) of benzaldehyde phenylhydrazone. Benzene (45 ml) is added to the dropping funnel, the flask is flushed with dry nitrogen, and then 15 ml of the benzene is added to the flask. To the dropping funnel is now added 0.214 gm (2.0 mole) of nitrosobenzene and the nitrosobenzene solution is added dropwise with stirring over a period of 20 min. Gas evolution is noted and the reaction is stirred for 2 hr. The reaction mixture is concentrated under reduced pressure to afford 0.197 gm (100%), m.p. 112–114°C.

## C. Alkylation of Oximes

The alkylation of oximes gives rise to a mixture of oxime ethers and nitrones as shown in Eq. [25].

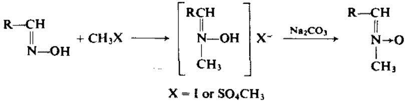


$$>C{=}NOH + RX \longrightarrow >C{=}NOR + >C{=}\underset{\substack{\downarrow\\ O}}{N}{-}R + HX$$

(25)

The percentage of the respective oxime ether and nitrone depends on the nature of the starting oxime, the alkyl halide, and the experimental conditions. For example, Smith and Robertson [19] reported a steric effect in the alkylation of various substituted benzophenone oximes in absolute ethanol where methyl bromide gave 11–47% nitrone and benzyl bromide gave only 4–23% [19]. The effect of the cations $Li^+$, $Na^+$, $K^+$, $(CH_3)_4N^+$ in the benzylation of benzophenone oxime salts in absolute ethanol was also shown to play a small role in changing the ratio of oxime ether to nitrone products [19]. Electron-withdrawing groups, R, in the alkylation of $(RC_6H_4)_2CNONa$ with benzyl bromide in absolute ethanol gave an increase in the percentage of *O*-alkyl oxime. Very little effect was noted when the substituents R were in $R{-}C_6H_4CH_2Br$ [19]. (Earlier it was reported that the higher the dissociation constant of the oxime, the higher is the yield of the obtained oxime ether [98].)

Brady [98] and co-workers earlier reported that dimethyl sulfate or methyl iodide reacts with *syn*-aldoximimes in the absence of solvent to give the salts of the nitrones. The nitrones are isolated in good yield upon further work-up (Eq. 26).

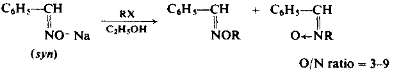


$$\begin{matrix}R{-}CH\\ \|\\ N{-}OH\end{matrix} + CH_3X \longrightarrow \left[\begin{matrix}RCH\\ \|\\ N{-}OH\\ |\\ CH_3\end{matrix}\right]X^- \xrightarrow{Na_2CO_3} \begin{matrix}R{-}CH\\ \|\\ N{\rightarrow}O\\ |\\ CH_3\end{matrix}$$

(26)

$X = I$ or $SO_4CH_3$

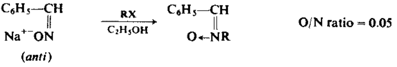
Recently Buehler [99] has shown that *anti*-benzaldoxime is readily N-alkylated by various alkyl halides, whereas *syn*-benzaldoxime is largely O-alkylated. These results offer a convenient route to $\alpha$-phenyl-*N*-substituted nitrones and *O*-alkyl benzaldoximes (Eqs. 27, 28).



$$\underset{(syn)}{\begin{matrix}C_6H_5{-}CH\\ \|\\ NO^-\,Na\end{matrix}} \xrightarrow[C_2H_5OH]{RX} \begin{matrix}C_6H_5{-}CH\\ \|\\ NOR\end{matrix} + \begin{matrix}C_6H_5{-}CH\\ \|\\ O{\leftarrow}NR\end{matrix}$$

(27)

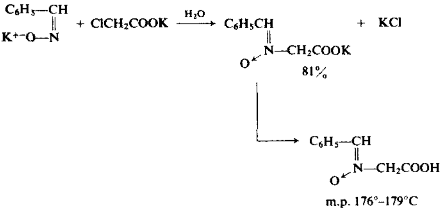
O/N ratio = 3–9



$$\underset{(anti)}{\begin{matrix}C_6H_5{-}CH\\ \|\\ Na^{+-}ON\end{matrix}} \xrightarrow[C_2H_5OH]{RX} \begin{matrix}C_6H_5{-}CH\\ \|\\ O{\leftarrow}NR\end{matrix}$$

O/N ratio = 0.05 (28)

Earlier Hantzsch and Wild [100] reported that *syn*- and *anti*-benzaldoxime react with chloroacetic acid to give *N*-(carboxymethyl)-α-phenylnitrone. Recently Schoenewaldt and co-workers [101] used the Hantzsch and Wild procedure to obtain an 81% yield of this nitrone, as shown in Eq. 29.

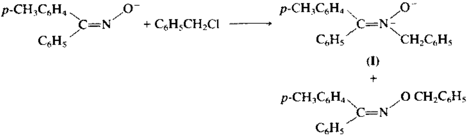


(29)

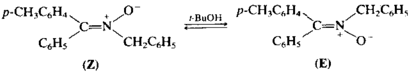
Treatment of various *syn*- or *anti*-benzaldoximes in methyl iodide in the presence of silver iodide has been reported by several investigators to give only *O*-methylation [89, 99, 102a].

Relatively mild conditions are preferred in the preparation of nitrones since it is well known that they undergo a thermal rearrangement to the only *O*-methylation [89,99,102a].

A kinetic investigation of the configurational isomerization of geometrically isomeric nitrones was reported by Dobashi, Goodnow, and Grubbs [102b]. The nitrones were prepared by the action of the benzophenone oxime and the benzyl chloride, as shown in Eq. 30. The isomerization of (I) is shown in Eq. 31 [102b].

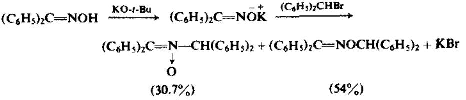


(30)



(31)

### *3-9. Preparation of* N*-Benzhydryl-α,α-diphenylnitrone* 103



$$(C_6H_5)_2C{=}NOH \xrightarrow{KO\text{-}t\text{-}Bu} (C_6H_5)_2C{=}\overset{-\ +}{NOK} \xrightarrow{(C_6H_5)_2CHBr}$$

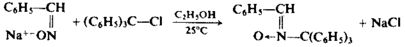
$$\underset{(30.7\%)}{(C_6H_5)_2C{=}\underset{\substack{\downarrow\\ O}}{N}{-}CH(C_6H_5)_2} + \underset{(54\%)}{(C_6H_5)_2C{=}NOCH(C_6H_5)_2} + KBr \qquad (32)$$

To a solution of 9.86 gm (0.05 mole) of benzophenone oxime in 80 ml of dry benzene is added 4.6 gm (0.041 mole) of potassium *t*-butoxide and the mixture refluxed for 1 hr. The benzene is distilled and when the vapor temperature reaches 80°C a benzene solution of 12.35 gm (0.05 mole) of benzhydryl is added. The total volume is adjusted with dry benzene to approx. 150 ml and the mixture is stirred and refluxed for 45 hr (see Note). At the end of this time the yellow salt of the oxime is entirely replaced by a fine white precipitate of potassium bromide. The hot suspension is filtered, the solid washed with acetone, and the combined washings concentrated under reduced pressure to afford an oil. Cooling affords a solid which upon recrystallization from ethanol gives 5.6 gm (30.7%), m.p. 162–166°C. The compound has a broad melting point, probably because it rearranges during the melting operation to benzophenone *O*-benzhydryloxime, m.p. 90–94°C.

Concentration of the mother liquors afforded an oil which upon crystallization from ethanol gave 9.85 gm (54%) of white crystals, m.p. 101.5–102°C (recrystallized from ethanol or methanol) identified as the *O*-oxime ether.

NOTE: It should be noted that this prolonged reflux time used by the authors of reference probably tends to lower the yield of the nitrone because of the competing thermal rearrangement to the *O*-oxime ether described earlier. This may be the reason for the lower yields of related nitrones reported recently by a similar procedure [104].

### *3-10. Preparation of α-Phenyl-*N*-triphenylmethylnitrone* [99]



$$\begin{matrix}C_6H_5{-}CH\\ \| \\ Na^{+}\,{}^{-}ON\end{matrix} + (C_6H_5)_3C{-}Cl \xrightarrow[25^\circ C]{C_2H_5OH} \begin{matrix}C_6H_5{-}CH\\ \| \\ O{\leftarrow}N{-}C(C_6H_5)_3\end{matrix} + NaCl \qquad (33)$$

Twenty milliliters of absolute ethanol is reacted with 0.23 gm (0.01 gm atoms) of sodium and then 1.21 gm (0.01 mole) of *anti*-benzaldoxime is added. To the resulting stirred solution is added 2.78 gm (0.01 mole) of triphenylmethyl chloride. The reaction mixture, which is slightly exothermic, is stirred for 10 min, cooled overnight, and then filtered to afford 3.0 gm (83%) of a crude white product, m.p. 132–134°C. Recrystallization from 80% ethanol affords 2.7 gm (75%) of pure product, m.p. 143–144°C, $\lambda_{max}^{C_2H_5OH}$ 252 m$\mu$, log $\epsilon$ 4.23; NMR 1.86 and 2.51$\tau$ (complex patterns).

## 4. MISCELLANEOUS METHODS

(1) Reaction of quaternary Mannich bases with aromatic nitroso compounds [105–108].

(2) Reaction of nitrosobenzene with quinones to give dinitrones [109].

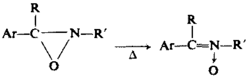
(3) Reaction of aromatic nitroso compounds with 1-benzyl-1,4-dihydronicotinamide to afford $\alpha$,*N*-diphenylnitrone [110].

(4) Dimerization of nitrones [111, 112].

(5) Aldol condensation reactions of nitrones to give substituted nitrones [8, 113].

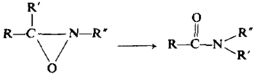
(6) Thermal cleavage of *N*-methyl-*N*-tetrahydropyranyl-(2)hydroxylamine to *N*-methyl C-4-hydroxymethylenenitrone [114].

(7) Thermal rearrangement of oxaziranes: The rearrangement of 3-aryl-oxizirane derivatives has been reported [6e, 115, 116, 117] to give the corresponding nitrones in 50–100% yields (Eq. 34)Bicyclic oxaziranes give similar results [118].



(34)

Nonaromatic oxaziranes tend to afford amides on thermal isomerization (Eq. 35) [63].



(35)

The starting oxaziranes may be prepared in 50–80% yield by the reaction of imines with a peracetic acid solution in methylene chloride at 10–20°C. The thermal rearrangement reaction of oxaziranes requires further study before it can be recommended as a general method for the preparation of nitrones.

(8) Condensation of diaryl ketimines and benzhydryl hydroxylamines [104].

(9) Bromination of nitrones [119].

(10) Aldol condensation products of nitrones [120].

(11) Reaction of nitroso compounds with 1,3-diketones [121].

(12) Reaction of nitroso compounds with diazo compounds [6b, 21, 122, 123].

(13) Reaction of sulfur ylides with nitrosobenzene [124].

(14) Reaction of nitroso compounds with olefins [125–129] and acetylenes [130–134].

(15) Reaction of nitroso compounds with quaternary Mannich bases [135–138].

(16) Reaction of nitroso compounds with 1-benzyl-1,4-dihydronicotinamide [139].

(17) Reaction of quinones with nitrosobenzenes [140].

(18) Preparation of triaryl nitrones by the reaction of diphenylacetonitrile and some nitrobenzenes in the presence of saturated KOH or MeONa in methanol [141].

(19) Preparation of nitrones by the reaction of methyleneanilines with aryl nitroso compounds [142a,b].

(20) Bridged bicycloalkanes via intramoleculer nitrone-olefin cycloaddition reactions [145].

(21) Nitrones by reaction of methylhydroxylamine sulfate with substituted imines [144].

(22) Nitrones via the alkylation of *O*-trimethylsilyloxime [145].

(23) Conversion of secondary amines to nitrones via the tungstate catalyzed oxidation of secondary amines with hydrogen peroxide [146].

(24) Preparation of nitrones of thio esters [147].

(25) Preparation of nitrones and nitroxides derived from oxazolines and dihydrooxazines [148].

(26) Substitution reactions on $C,N$-diaryl nitrones [149].

(27) Four-membered nitrones [150].

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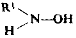
## 1. INTRODUCTION

The earliest report of substituted hydroxylamines goes back to 1865 [1]. The methods of synthesis of hydroxylamines are quite diverse and a few are of a general nature. Interest in developing satisfactory synthetic methods for the various types of substituted hydroxylamines was quite low until relatively recently when medicinal or biochemical interests arose for the O-substituted hydroxylamines. As a result, a number of new techniques have been developed for the preparation of O-substituted hydroxylamines, while methods of preparation of N-substituted compounds, with a few exceptions, have not developed much beyond those known about the time of World War I.

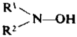
The only review article on the subject emphasizes the O-substituted hydroxylamines [2].

Other reviews are to be found in standard monographs [3–5]. Of these, Lesbre [3] covers the older literature only up to approximately 1930, while Smith [4] and Millar and Springall [5] cite references as recent as 1965.

The types of substituted hydroxylamines discussed here may be represented by the following structural formulas:


$\mathrm{R^1(H)N{-}OH}$

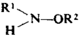
(I)


$\mathrm{R^1(R^2)N{-}OH}$

(II)

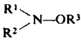
$\mathrm{NH_2{-}OR^1}$

(III)


$\mathrm{R^1(H)N{-}OR^2}$

(IV)

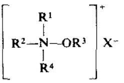
and


$\mathrm{R^1(R^2)N{-}OR^3}$

(V)

R, $R^1$, $R^2$, $R^3$ = alkyl, aryl, or aralkyl

The quaternary salts derived from structures (II) and (V) will not be discussed here. It should be noted that the quaternary salt derived from structure (V) is identical with the salts obtained by reaction of tertiary amine oxides with alkyl halides (structure VI).



$$\left[ R^2-\overset{\displaystyle R^1}{\underset{\displaystyle R^4}{N}}-OR^3 \right]^+ X^-$$

(VI)

The various methods of synthesis of N- and O-substituted hydroxylamines are shown in Schemes 1–6. Not all of these methods are practical but are listed here for reference only.

Scheme 1 shows the interrelationship of a number of the synthetic procedures with various alkyl- and aralkyl-substituted hydroxylamines. Some of the reactions are shown in simplified form. The stepwise N-alkylation of unsubstituted hydroxylamine usually cannot be stopped at the monoalkylated stage if the alkylating agent is of low molecular weight. The preparation of such monoalkylated hydroxylamines is difficult. The most general method for preparing them, albeit in small quantities, involves the reduction of oximes or of nitronate salts with diborane. *N*-Aromatic hydroxylamines are frequently prepared by the reduction of aromatic nitro or nitroso compounds with zinc and aqueous ammonium chloride (Scheme 2). Also used for the preparation of N-substituted hydroxylamine is the Grignard reaction with nitrosyl chloride (Scheme 3).

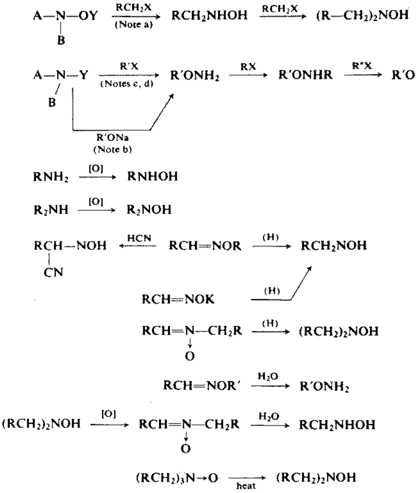
N,N-Disubstituted hydroxylamines may be prepared by direct alkylation of hydroxylamine (Scheme 1) or by alkylation of N-monosubstituted hydroxylamine, by reduction of nitrones, benzoyloxylation of secondary amines (Scheme 1), Grignard reactions with quinone monooximes or monoimines, with nitrones, with C-nitroso compounds, with nitrate esters, and with esters of nitronic acids (Scheme 3), by the Michael addition of hydroxylamine with *N*-alkylhydroxylamine (Scheme 4) and by the thermal decomposition of certain amine *N*-oxides or their derivatives (Schemes 1 and 5).

O-Substituted hydroxylamines have been prepared by a variety of methods. Many involve reagents in which the reactive hydrogens on the nitrogen of hydroxylamine have been blocked. They also have been prepared by the hydrolysis of *O*-alkyloxime ethers (Scheme 1), the Michael addition of N,N-disubstituted hydroxylamine and of hydroximate esters to activated olefins (Scheme 4) and, in a few specific cases, by the rearrangement of N,N-disubstituted amine-*N*-oxides (Scheme 6).

Scheme 1 indicates that N- and N,N-disubstituted O-substituted hydroxylamines may be prepared by alkylation of *O*-alkylhydroxylamine

## SCHEME 1

Methods of Preparation of Substituted Hydroxylamines



*Notes to Scheme* 1:

(a) $A = H, B = Y = SO_3H$ or

$A = C_2H_5O\overset{\overset{O}{\|}}{C}; B = Y = H$ (neutral or acid conditions) or

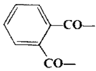
$A = B = H; Y = H$

(b) $A = B = H; Y = Cl$

(c) $A = B = SO_3H; Y = OH$

(d) $A = C_2H_5O\underset{\underset{O}{\|}}{C}—, B = H, Y = OH$ (basic conditions) or

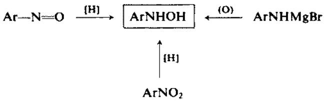
A = B =



or $CH_3—\underset{\underset{OC_2H_5}{|}}{C}=$ (under basic conditions)

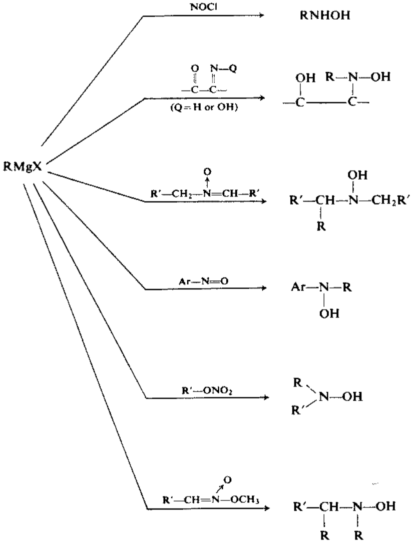
## SCHEME 2

Methods of Preparing *N*-Arylhydroxylamines

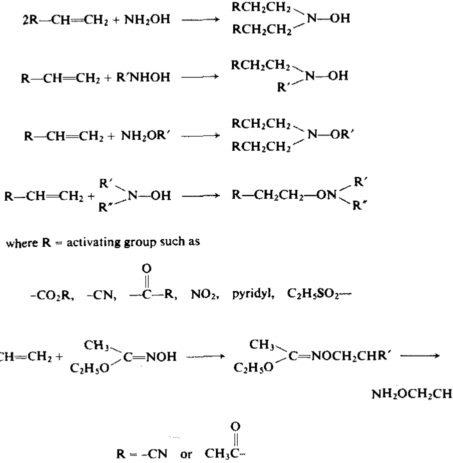


## SCHEME 3

Reactions of Grignard Reagents to Prepare Hydroxylamines



SCHEME 4
Michael Addition Reactions

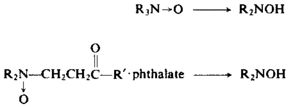


where R = activating group such as

$-CO_2R$, $-CN$, $-\overset{O}{\overset{\|}{C}}-R$, $NO_2$, pyridyl, $C_2H_5SO_2-$

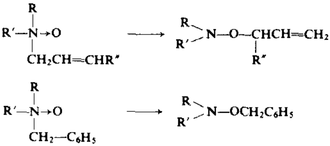
R = -CN or $CH_3\overset{O}{\overset{\|}{C}}-$

SCHEME 5
Thermal Decomposition of Tertiary Amine *N*-oxides and Their Derivatives



and by dialkylation of ethyl *N*-hydroxycarbamate under basic conditions. Scheme 1 also shows the preparation of α-hydroxylaminonitriles. Trisubstituted compounds may be prepared by alkylation of *N*,*O*-dialkylhydroxylamine. The Michael addition of *N*,*N*-dialkylhydroxylamine or of *O*-alkyl-

SCHEME 6
Rearrangement of *N*-"Allyl"-*N,N*-dialkylamine *N*-Oxides



hydroxylamine to active olefines leads to N,N,O-substituted compounds (Scheme 4).

## A. Nomenclature

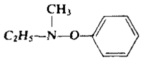
Prior to 1937, *Chemical Abstracts,* in line with the general practice in the literature, name *O*-alkyl substituted hydroxylamines "*alpha*-alkylhydroxylamines" and *N*-alkyl substituted hydroxylamine, "*beta*-hydroxylamines." Both classes were indexed under "hydroxylamines."

In 1945, *Chemical Abstracts* adopted IUPAC Rule 35, which states in effect that compounds derived from hydroxylamine by replacement of the hydrogen of the hydroxyl group will be regarded as alkoxy derivatives and are indexed as alkoxyamines. Compounds derived by replacement of the hydrogens of the amino group are called alkylhydroxylamines and indexed as "hydroxylamines, alkyl" [6a].

In 1962, *Chemical Abstracts* expanded the above rule so that *N,O*-dialkylhydroxylamines began to be indexed as alkoxyalkylamines rather than as alkylalkoxyamines [6b].

For example, under the present *Chemical Abstract* rules, $CH_3NHOCH_3$ is indexed as *N*-methoxymethylamine (with a cross reference to *N,O*-dimethylhydroxylamine).

In this chapter, we believe that a simpler system is more suitable to show the relationship of the substituents of a hydroxylamine. The following example illustrates the nomenclature system usually used here.

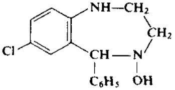


(VII)

In our system, Structure VII would simply be called *N*-ethyl-*N*-methyl-*O*-phenylhydroxylamine. To be noted is that, unlike some nomenclature systems found in the literature, we give precedence to N over O and ethyl over methyl on an alphabetical basis.

In some complex structures, the "hydroxylamino" prefix is found in the literature. When used, the bonding to the substituent is always through the nitrogen atom.

In some names, the only clue that we may be dealing with the hydroxylamine function is the fact that a hydroxyl group is indicated to be on a nitrogen. For example, an extreme case, which may be considered a substituted hydroxylamine:



7-Chloro-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine

Simple heterocyclic compounds such as *N*-hydroxymorpholine or 1-hydroxypiperidine are hydroxylamine derivatives. For such compounds we usually conform to the literature practice.

## B. Safety Notes

In the discussion to follow, hydroxylamine or its salts are subjected to a variety of reactions. It has recently been found that hydroxylamine, salts of hydroxylamine, as well as solutions containing these compounds may explode. The causes of these explosions are not well understood [6c]. Whether the various substituted hydroxylamines represent explosion hazards is not known. It is recommended that precautions against explosions be taken whenever hydroxylamine, substituted hydroxylamines, their salts, or their solutions are handled.

## C. Uses

Diethylhydroxylamine has been suggested as a stabilizer for color formation for monoalkylphenols [6d] and phenolic antioxidants [6e]. It has also been reported to stabilize emulsions used in the latex industry [6f] and for Spandex rubber [6g], as well as a reducing agent for quinones [6h] and a monomer stabilizer [6i] or inhibitor [6j,k]. Many other applications appear in the literature, and the compound is commercially available from Pennwalt Corporation.

## 2. CONDENSATION REACTIONS

### A. Alkylation of Hydroxylamine and Substituted Hydroxylamines

The reaction of hydroxylamine with alkyl halides or dialkyl sulfates arose by analogy to the alkylation of amines. It was found earlier, however, that products of the reaction are more difficult to predict than those obtained from ammonia or amines.

For example, the treatment of a concentrated solution of 1 mole of hydroxylamine in methanol with 1 mole of methyl iodide gave rise to the hydroiodide salt of *N*,*N*-dimethylhydroxylamine [7]. Under only slightly different reaction conditions, methyl iodide reacted with a hydroxylamine solution (possibly containing some sodium methylate) to produce the hydroiodide salt of trimethylamine oxide (m.p. 127°C dec.; sulfate salt, m.p. 155–156°C; hydrochloride salt, m.p. 205–210°C; dihydrate of free base, m.p. 96°C; chloroplatinate, m.p. 228–229°C; aurichloride, m.p. 200°C; picrate, m.p. 196–197°C. Upon further treatment with methyl iodide at elevated temperatures, this trialkylamine oxide is converted to *N*,*N*,*N*,*O*-tetramethylhydroxylammonium iodide. At room temperature this reaction proceeds only very slowly [8].

On the other hand, when a similar reaction is carried out with ethyl iodide, the product isolated (after neutralization of hydroiodide salt) was only the *N*,*N*-diethylhydroxylamine (b.p. 130–134°C; $d_{15}^{15}$ 0.8771; oxalate salt, m.p. 136–137°C) and not the triethylamine oxide expected on the basis of the experience with methyl iodide. Isopropyl and *n*-propyl iodide behaved in a similar manner [8]. *Only when N,N-diethylhydroxylamine* was treated with additional ethyl iodide, was triethylamine oxide hydroiodide formed (picrate, m.p. of 164°C). Ethyl chloride was relatively unreactive in these reactions.

From these early observations, it appears that as the alkylating agent increases in molecular weight, there is a greater likelihood for stepwise alkylation and, perhaps more important, *O*-alkylation takes place at the last stage of alkylation. These data may be roughly represented by Eqs. (1) and (2).

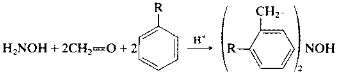
$$\mathrm{NH_2OH} \xrightarrow{\mathrm{RX}} \mathrm{RNHOH} \xrightarrow{\mathrm{RX}} \mathrm{R_2NOH} \xrightarrow{\mathrm{RX}} [\mathrm{R_3NOH}]^+\ \mathrm{X}^- \tag{1}$$

$$[\mathrm{R_3NOH}]^+\ \mathrm{X}^- \xrightarrow{\mathrm{OH}^-} \mathrm{R_3N}\rightarrow\mathrm{O} \xrightarrow{\mathrm{RX}} [\mathrm{R_3N{-}OR}]^+\ \mathrm{X}^- \tag{2}$$

By a similar technique, 2 moles of *p*-chlorobenzyl chloride have been reacted with hydroxylamine to produce *N*,*N*-di(*p*-chlorobenzyl)hydroxylamine (m.p. 121–122°C). This alkylation also appears to proceed stepwise [9a,b].

A typical example of this procedure is the preparation of *N*-(*p*-chlorophenyldiphenylmethyl)hydroxylamine (Preparation 2-1). As is frequently found in the literature, the first step of the reaction involves the generation of hydroxylamine from hydroxylamine hydrochloride in alcoholic solution using sodium metal [10, 11] or sodium carbonate [12a,b]. The preparation of a dialkylhydroxylamine is given in Preparation 2-2.

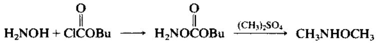
Hydroxylamine can also be alkylated by the reaction of formaldehyde with activated aromatics, as shown in Eq. 3 [12c].



(3)

Hydroxylamine can also be reacted with chlorotriazines (such as cyanuric chloride), to give substituted hydroxylamines [12d].

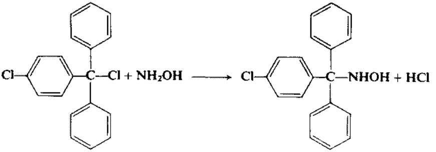
Hydroxylamine can be converted to *N*-alkyl-*O*-alkyl hydroxylamine by reacting hydroxylamine with butyl chloroformate followed by reaction with dimethyl sulfate (see Eq. 4) [12e].



$$H_2NOH + Cl\overset{O}{\overset{\|}{C}}OBu \longrightarrow H_2NO\overset{O}{\overset{\|}{C}}OBu \xrightarrow{(CH_3)_2SO_4} CH_3NHOCH_3 \qquad (4)$$

### 2-1. *Preparation of* N-(p-*Chlorophenyldiphenylmethyl)hydroxylamine* [11]

$$NH_2OH \cdot HCl + NaOC_2H_5 \xrightarrow{C_2H_5OH} NH_2OH + NaCl + C_2H_5OH \qquad (5)$$



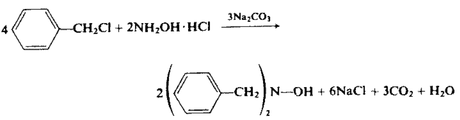
(6)

To a warm solution of 10.2 gm (0.147 mole) of hydroxylamine hydrochloride in 200 ml of absolute ethanol is cautiously added a solution of 3.2 gm (0.139 gm-atom) of sodium in 60 ml of absolute ethanol. The resultant mixture is then cooled to 0°C and a solution of 15.6 gm (0.05 mole) of *p*-chlorophenyldiphenylmethyl chloride in 250 ml of ether (peroxide free) is added while maintaining the low reaction temperature (use an inert atmosphere). After 1 hr, water is added to the reaction mixture to dissolve inorganic salts. The aqueous layer is separated and discarded. The ether layer is washed with cold water, dried with calcium chloride, and filtered. In a hood, with an appropriate gas trap, gaseous hydrogen chloride is bubbled through the ether solution until two layers form. At this point, the gas addition is stopped and a small quantity of water is added to the reaction system with shaking. The white crystalline solid which forms is filtered off and washed with ether (preferable to have a peroxide-free grade or a different solvent). The solid is covered with ether and stirred vigorously with 10% aqueous sodium hydroxide for 10 hr or until no more solid remains. The ether layer is separated and evaporated to dryness. The resultant crystals are washed with ether and dried to afford 12.1 gm (78%), m.p. 80–108°C. This product is quite sensitive to air. It may be crystallized from dry ether–petroleum ether mixture. The product is not stable on storage.

By techniques similar to Preparation 2-1 *N*-triphenylmethylhydroxylamine (m.p. 124–135°C) [10], *N*-(*p*-methoxyphenylphenylmethyl)hydroxylamine (m.p. 100–111°C dec.), and *N*-(*p*-nitrophenyldiphenylmethyl)-hydroxylamine (m.p. 147–161°C dec.) have been prepared [11]. As may be seen from the melting points, these compounds are probably quite impure.

While there appears to be little difficulty in preparing *N*-monoalkylhydroxylamines, if the alkyl group is large and bulky, as illustrated above, monoalkylation with smaller alkyl moieties is difficult. An elegant technique to overcome this problem, involves the deliberate dialkylation of hydroxylamine, oxidation of the product to the corresponding nitrone (see Chapter 9, Table I and also Section 2), followed by hydrolytic cleavage of the nitrone [12a,b]. Examples illustrating the use of this method are shown in Preparations 2-4 and 2-5.

### *2-2. Preparation of* N,N*-Dibenzylhydroxylamine by Dialkylation* [12a]



(7)

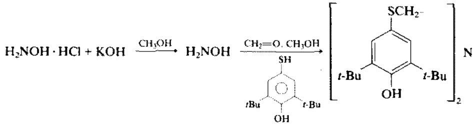
A mixture of 14 gm (0.202 mole) of hydroxylamine hydrochloride and 50 gm (0.395 mole) of benzyl chloride in 200 ml of 70% ethanol is treated with 60 gm of crystalline sodium carbonate. The mixture is heated under a reflux condenser for 2 hr, cooled to room temperature, filtered, and the solids discarded. The filtrate is treated with sufficient ice water to cause precipitation of *N,N*-dibenzylhydroxylamine. The reaction mixture is then thoroughly cooled in a freezing mixture to permit complete precipitation of product to take place. The yield, upon filtration, is 26 gm (61.5%), m.p. 123°C. A similar preparation has recently been reported [13a].

### 2-3. *Preparation of Bis(2-methoxyethyl)hydroxylamine and 2-Methoxyethylhydroxylamine* [124]

$$NH_2OH \cdot HCl + 2CH_3OCH_2CH_2I \xrightarrow[\substack{DMSO \\ H_2O}]{NaHCO_3} (CH_3OCH_2CH_2)_2NOH + CH_3OCH_2CH_2NHOH \qquad (8)$$

To a solution of 5.75 gm (0.0825 mole) of hydroxylamine hydrochloride in 25 ml of dimethylsulfoxide (DMSO) and 1.0 ml of water in a 3-necked round bottom flask equipped with a mechanical stirrer, a thermometer, and a condenser is added 22.7 gm (0.27 mole) of sodium bicarbonate. The mixture is stirred and a stream of nitrogen kept throughout the reaction. To this solution is added 33.8 gm (0.182 mole) of 2-methoxyethyl iodide and the stirring continued at 35°C for 20 hr. The temperature is then increased to 50°C, and kept at this temperature for 4 hr. The mixture is made pH 8 by means of 50% sodium hydroxide and extracted several times with 100-ml portions of toluene (original procedure uses benzene), then filtered, and the solids are washed again with toluene. The extracts are dried and concentrated to give 37.0 gm of an oil, which contains (as determined by gas chromatography) 23.0% of bis(3-methoxyethyl)hydroxylamine (62.7% overall yield) and 9.0% of 2-methoxyethylamine (20.1% yield).

### 2-4. *Preparation of* N,N-*Bis(3,5-di-*t*-butyl-4-hydroxyphenylthiomethyl) hydroxylamine* [12g]



(9)

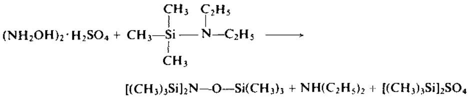
To a 3-necked round bottom flask equipped with a mechanical stirrer, a condenser, a dropping funnel, a nitrogen inlet–outlet, and a thermometer is added 3.47 gm of hydroxylamine hydrochloride (0.05 mole) and 20 ml of methanol. The mixture is stirred at 0°C while a solution of 3.07 gm (0.055 mole) of potassium hydroxide in 50 ml of methanol is added. Then 8.2 ml of 37% aqueous formaldehyde (0.11 mole) is added, followed by a solution of 23.84 gm (0.10 mole) of 3,5-di-*t*-butyl-4-hydroxythiophenol in 100 ml of methanol. The reaction mixture is stirred at ambient temperature for 8 hr followed by the addition of 75 ml of water. The precipitated product is filtered and then recrystallized from *n*-heptane to give 19.5 gm (73.2% yield) of a white solid, m.p. 135–138°C.

Analysis: Calculated for $C_{30}H_{47}NO_3S_2$: C, 67.5; H,8.9; N2.6;
Found: C,67.7; H,8.8; N,2.5.

Because of its simplicity, the direct alkylation of hydroxylamine has been attempted with a large variety of reagents [13a–16]. For example, 1-bromo-2-propyne has been reacted in strong caustic aqueous media with hydroxylamine to produce *N*-2-propynylhydroxylamine [melting point of hydrochloride salt, 162°C dec] [13b]; $\beta$-halo-$\alpha$-tetralones have been reacted to produce $\beta$-hydroxylamino-$\alpha$-tetralonoxime [14]; 6-chlorouracil has been reacted to produce 6-hydroxylaminouracil [15]; and $\alpha$-bromocarboxylic acids give $\alpha$-hydroxy amino acids [16–18].

Pyridine, alcohol, and water are the reaction medium which allows ethyl bromide to react with *N*-phenylhydroxylamine at 25°C to give *N*-ethyl-*N*-phenylhydroxylamine in 29% yield [19]. Other examples by similar technique have been reported earlier [8–20]. However, this method is not generally useful since *N*-methyl-*N*-phenylhydroxylamine could not be prepared [20].

Trialkylsilyl chlorides usually produce only mono- and disilylated hydroxylamines. However, diethyl (trimethylsilyl)amine reacts readily with hydroxylamine to produce *N*,*N*,*O*-tris(trimethylsilyl)hydroxylamine in good yield (Eq. 6) [21].



$$(NH_2OH)_2\cdot H_2SO_4 + CH_3{-}\overset{CH_3}{\underset{CH_3}{Si}}{-}\overset{C_2H_5}{N}{-}C_2H_5 \longrightarrow$$

$$[(CH_3)_3Si]_2N{-}O{-}Si(CH_3)_3 + NH(C_2H_5)_2 + [(CH_3)_3Si]_2SO_4 \qquad (10)$$

(NOTE: This equation was purposely left unbalanced because the stoichiometry may not have been completely developed.)

Normally, alkylation procedures for the preparation of *N,N,O*-trialkylhydroxylamines require the use of *O*-alkylhydroxylamines (alkoxyamines) as one of the starting materials [22, 23] or the use of *N,O*-dialkylhydroxylamines, which may be formed by other methods [24–26]. While these procedures are relatively old, they have been used without significant modification fairly recently.

As may be anticipated, the reaction of $\alpha,\omega$-dibromoalkane with *O*-alkylhydroxylamines produces cyclic products which are N,N,O-trisubstituted hydroxylamines. For example, by reacting *O*-methylhydroxylamine (methoxyamine) with 1,5-dibromopentane, *N*-methoxypiperidine is formed (40% yield, b.p. 25–26°C/8 mm Hg; $n_D^{20}$ 1.4382) [22].

Other polysubstituted hydroxylamines prepared by this general procedure are *N,N*-dibenzyl-*O*-ethylhydroxylamine, b.p. 176–178°C (18 mm), hydrochloride salt m.p. 145–146°C [23]; *N,O*-diethyl-*N*-methylhydroxylamine, b.p. 90°C, chloroplatinate salt, m.p. 158°C); *N,N,O*-trimethylhydroxylamine, b.p. 30°C, hydrochloride salt, m.p. 123°C, chloroplatinate salt, m.p. 159°C) [24, 25].

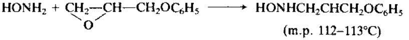
In a patent [27] *O*-alkylation of *N,N*-dialkylhydroxylamines is mentioned. In this case, *N,N*-dimethylhydroxylamine is treated with butyl iodide in ether solution at room temperature. The free *N,N*-dimethyl-*O*-butylhydroxylamine is reported to have a boiling range of 110–112°C. The same patent reports the boiling range of *N,N*-dimethyl-*O*-*n*-propylhydroxylamine as 80.5–82°C; however, it was produced by hydrogenation of the corresponding *O*-allyl derivative [27].

A recent report mentions that trimethylsilyl chloride reacts with *N,N*-bis(trifluoromethyl)hydroxylamine to produce *N,N*-bis(trifluoromethyl)-*O*-trimethylsilylhydroxylamine [28].

## B. Ethoxylation of Hydroxylamine

Only a limited amount of research had been reported on the reaction of ethylene oxide derivatives with hydroxylamine or its derivatives. For example, propylene oxide has been reacted with *N*-hydroxypiperidine [29].

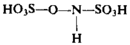
Glycidyl phenyl ether has also been reacted with an excess of hydroxylamine to afford *N*-substituted hydroxylamines [30] (Eq. 11).



$$\mathrm{HONH_2} + \underset{\diagdown\ \mathrm{O}\ \diagup}{\mathrm{CH_2{-}CH}}\mathrm{{-}CH_2OC_6H_5} \longrightarrow \underset{\text{(m.p. 112–113°C)}}{\mathrm{HONHCH_2CHCH_2OC_6H_5}} \qquad (11)$$

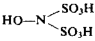
### C. Reactions with Hydroxylaminesulfonic Acids

The salts of several sulfonic acid derivatives of hydroxylamine are known. Our concern here is with three of these:



$HO_3S{-}O{-}\underset{\displaystyle H}{\underset{|}{N}}{-}SO_3H$

Hydroxylamineisodisulfonic acid

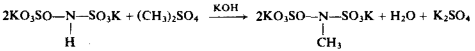


Hydroxylaminedisulfonic acid

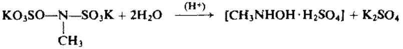
$H_2N{-}O{-}SO_3H$

*Hydroxylamine-O-sulfonic acid*

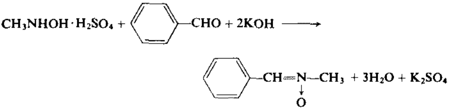
In strongly alkaline solution the basic potassium hydroxylamineisodisulfonate is formed from the isodisulfonate salt. This salt has been *N*-alkylated with dimethyl sulfate or methyl iodide. By a somewhat complex technique, involving, *inter alia*, nitrone formation, *N*-alkylhydroxylamines can be isolated (Eqs. 12–15) [31].



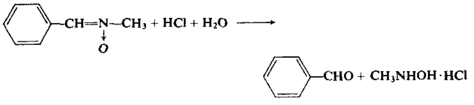
$$2KO_3SO{-}\underset{\displaystyle H}{\underset{|}{N}}{-}SO_3K + (CH_3)_2SO_4 \xrightarrow{KOH} 2KO_3SO{-}\underset{\displaystyle CH_3}{\underset{|}{N}}{-}SO_3K + H_2O + K_2SO_4 \qquad (12)$$



$$KO_3SO{-}\underset{\displaystyle CH_3}{\underset{|}{N}}{-}SO_3K + 2H_2O \xrightarrow{(H^+)} [CH_3NHOH \cdot H_2SO_4] + K_2SO_4 \qquad (13)$$



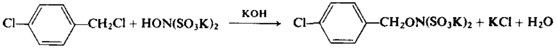
(14)



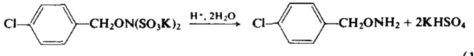
(15)

Unlike the salts of hydroxylamineisodisulfonic acid, which permit *N*-alkylation, salts of hydroxylaminedisulfonic acid are useful for the preparation of *O*-alkylhydroxylamine. The method of preparation is indicated in Eqs. 16, 17, and 18. The preparative procedure is similar to that used in the alkylation of potassium hydroxylamineisodisulfonate, although the isolation of the final product by use of a nitrone does not seem to be necessary [32–35a].

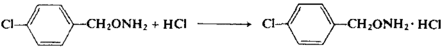
### 2-5. *Preparation of O-(4-Chlorobenzyl)hydroxylamine Hydrochloride (4-Chlorobenzyloxyamine Hydrochloride)* [35b]



(16)



(17)



(18)

To a solution of 83.7 gm (1.5 moles) of potassium hydroxide in 560 ml of water is added in turn with stirring, 300 gm (0.985 mole) of dipotassium hydroxylaminedisulfonate and 161 gm (1.0 mole) of 4-chlorobenzyl chloride. The stirred mixture is heated on a steam bath for 1.75 hr. After cooling, the precipitate is filtered off and refluxed for 3 hr in 1000 ml of 1.5 *N* sulfuric acid. The reaction mixture is then cooled and made strongly alkaline with a 15% aqueous sodium hydroxide solution. The mixture is then extracted with ether repeatedly. The ether extracts are combined and evaporated to dryness. The solid residue (crude free base, 80 gm, i.e., 51.5% of theory, m.p. 35–38°C) is taken up in 1 liter of ether. Anhydrous hydrogen chloride is bubbled through this solution to precipitate the hydrochloride salt. The yield is 59 gm (31%, overall), m.p. 243–244°C (dec.); the free base has b.p. 100°C/1 mm Hg.

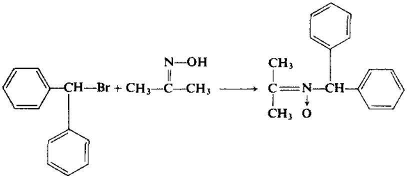
In this preparation, the hydrolysis of the alkylated dipotassium hydroxylaminedisulfonate with only 1 liter of 1.5 *N* sulfuric acid seems somewhat skimpy. We suggest that a higher level of sulfuric acid be considered at that stage of the reaction, if the alkylation has indeed gone to completion. Once the *O*-alkylhydroxylamine has been prepared by this reaction, it may be *N*-alkylated to produce an *N*,*O*-dialkylhydroxylamine [34].

The preparation of *O*-phenylhydroxylamine has been a synthetic challenge for some time since it is quite unstable. Using hydroxylamine-*O*-sulfonic acid. A small quantity of this compound has been prepared [36]. Reaction conditions probably require further study to improve the yield. Extension of the reaction to the preparation of *O*-alkylhydroxylamines would be of interest.

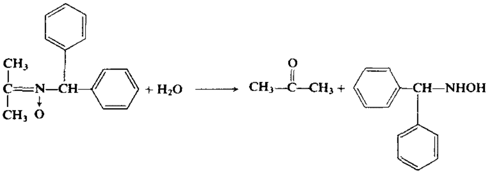
### D. Hydrolysis of Nitrones

As described earlier in this chapter, monoalkylhydroxyamines can be obtained by dialkylation (Preparation 2-2), oxidation of the resulting dialkylhydroxylamine to the nitrone, and then hydrolysis. This method is illustrated in Preparation 2-4.

*N*-Alkylation of oximes also affords nitrones which, if desired, can be hydrolyzed to hydroxylamine derivatives [9a, 37], as shown in Eqs. 19 and 20 and Preparations 2-6 and 2-7.

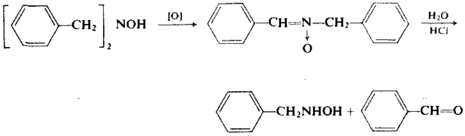


(19)



(20)

### *2-6. Preparation of* N*-Benzylhydroxylamine* [12a,b]



(21)

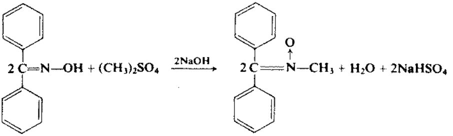
(*a*) *Preparation of α-phenyl-N-benzylnitrone* [12b]. To a flask equipped with a stirrer and condenser and containing 17.6 gm (0.0827 mole) of

*N,N*-dibenzylhydroxylamine is added 36.8 gm (0.17 mole) of yellow mercuric oxide and 100 ml of ether. The mixture is stirred and the resulting exothermic reaction causes the ether to reflux for 1 hr. After a total of 3 hr reaction time the reaction mixture is filtered and concentrated to afford 15.7 gm (90%), m.p. 81.5–83.5°C (recrystallized from acetone-ligroin).

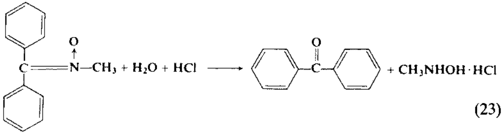
Jones and Sneed [12a] earlier reported that air-KOH can also be used to effect this oxidation.

(*b*) *Hydrolysis of α-phenyl-N-benzylnitrone to N-benzylhydroxylamine* [12a]. To a flask containing 17.0 gm (0.0806 mole) of the above nitrone is added 34 ml of concentrated hydrochloric acid solution. Then the mixture is steam-distilled to remove the formed benzaldehyde. After the benzaldehyde is removed the hydrochloric acid is removed by heating over a low flame. To the cool residue is added a cold solution of sodium carbonate to neutralize the mixture. The mixture is filtered, and the filtrate, after being cooled to 0°C, is made alkaline. After 1 hr *N*-benzylhydroxylamine precipitates from the cold filtrate and is filtered to afford 6.0 gm (61%), m.p. 57°C (recrystallized from benzene-petroleum ether). Yields as high as 88% have been reported for this preparation [12b].

### 2-7. *Preparation of* N-*Methylhydroxylamine Hydrochloride* [38a]



(22)



(23)

A mixture of 40 gm (0.2 mole) of benzophenone oxime, 70 ml of methanol, and a solution of 33 gm (0.8 moles) of sodium hydroxide in 180 ml of water is warmed gently with stirring until a clear solution has been produced. The solution is cooled and, with vigorous stirring, 40 gm (0.32 mole) of dimethyl sulfate (caution, toxic reagent) is added dropwise over a 2-hr period. The reaction mixture is cooled in an ice bath overnight. The nitrone is extracted from the cold reaction mixture with ether. The ether solution is dried with anhydrous sodium sulfate and filtered. The filtrate is evaporated to dryness. The residue is stirred with 300 ml of petroleum ether (b.p. 30–50°C) until it becomes powdery (crude yield 22 gm). Upon crystallization from ligroin (b.p. 60–70°C), approximately 20 gm (47.4%) of $\alpha,\alpha$-diphenyl-*N*-methylnitrone is isolated, m.p. 102–103°C.

A mixture of 2 gm (0.01 mole) of $\alpha,\alpha$-diphenyl-*N*-methylnitrone and 50 ml of 8% hydrochloric acid is refluxed for 15 min. The aqueous solution is evaporated under reduced pressure. The crude residue is dissolved in absolute alcohol. By fractional precipitation with absolute ether, 1.68 gm of benzophenone (m.p. 47–48°C) and 0.75 gm (95%) of *N*-methyldroxylamine hydrochloride (m.p. 87–89°C) are isolated.

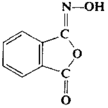
The free base has been prepared by treating the hydrochloride salt with potassium hydroxide pellets and distilling repeatedly in high-vacuum train equipment [25]. The properties of *N*-methylhydroxylamine are reported as m.p. 38.5°C, b.p. 115.0°C/760 mm Hg [25].

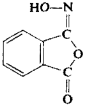
Recently, hydroxylamino acids have been prepared by hydrolysis of nitrones [38b]. The method is based on the ease of nitrone formation upon reaction of sodium *anti*-benzaldoxime with bromocarboxylates. This reaction is said to offer several advantages over the direct nucleophilic displacement of bromocarboxylates with hydroxylamine. In this latter case, hydroxylamine may act not only as a nucleophilic reagent or as a reducing agent but also as an oxidizing agent (in which case it may be thought of as an amide of hydrogen peroxide) [39]. Consequently the formation of hydroxylamino acids may be decreased in favor of the formation of oximino acid derivatives. This type of reaction is prevented when the critical parts of the hydroxylamine molecule are blocked. The acid hydrolysis of nitrones is readily accomplished and the hydroxylamino acids are readily isolated by neutralization to the isoelectric point. Another advantage is that the presence of the product in the reaction mixture can be detected with Fehling's solution. Obviously this technique would not be applicable to a reaction system which contains free hydroxylamine from the beginning, since hydroxylamine also reduces Fehling's solution.

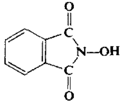
### E. *O*-Alkylation of Oximes and Hydrolysis of *O*-Alkyl Oximes

As may be expected from the foregoing discussion on the hydrolysis of nitrones, which produces *N*-alkylhydroxylamines, *O*-alkyl oximes, on hydrolysis, afford *O*-alkylhydroxylamines. It will be recalled that the stereochemistry of oximes was not settled until approximately 1925 (see

Chapter 11, Oximes). Consequently the relation of the course of the alkylation of oximes to their structure was not fully appreciated. In fact, only quite recently has it been shown that upon alkylation, *anti*-benzaldoximes yield nitrones (N-alkylation) while *syn*-benzaldoximes produce largely *O*-alkyl oximes [40]. To compound difficulties, some of the early work was done with phthaloximes at a time when it apparently was difficult to differentiate between the structures shown [41]:


(VIII)


(IX)

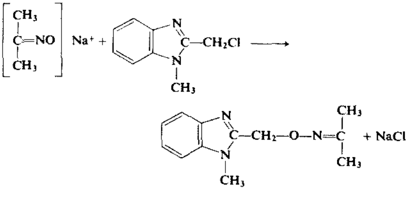

(X)

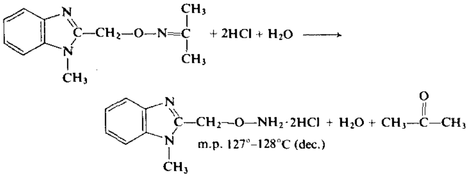
As late as 1928, the structures of (VIII) and (IX) had not been settled, although the present concepts of the geometry of *syn*- and *anti*-oximes had been accepted [42a]. In any case, at that time "yellow" phthaloxime was O-alkylated with methyl iodide and with dimethyl sulfate. Upon acid hydrolysis *O*-methylhydroxylamine hydrochloride (m.p. 149–151°C) was isolated [42a]. More recently it has been shown that the starting material used in that preparation actually was *N*-hydroxyphthalimide (structure X) and that structures (VIII) and (IX) were incorrectly assigned [42b].

The whole question of the effect of geometric isomerism on alkylation of oximes was avoided when the use of acetoxime [43, 44] was introduced.

In a review of the chemistry of substituted hydroxylamine it was suggested that the use of amidoximes instead of oximes may be a more convenient method of preparing these compounds [45]; however, no recent examples of this method were noted.

The acid hydrolysis of *O*-alkyl oximes may also be carried out by steam distillation rather than by refluxing the reaction mixture. By this means, 1-methyl-2-(aminooxymethyl)benzimidole dihydrochloride has been isolated when prepared according to Eqs. (24) and (25) [46].


(24)

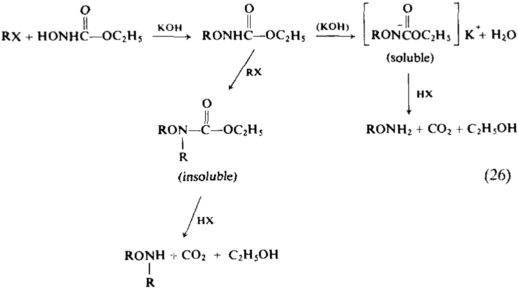


(25)

At least one group of investigators considered the O-alkylation of acetoxime as the method of choice for the preparation of *O*-aralkylhydroxylamines [46]. Only when this procedure gave inadequate results did they resort to other methods for the preparation of O-substituted hydroxylamines. This method has one advantage because acetoxime is readily accessible, whereas some of the other starting reagents (such as ethyl hydroxycarbamate, benzohydroxamic acid, and *N*-hydroxyphthalimide) are either quite expensive, require more complex syntheses of their own, or are of high molecular weight.

### F. *N*- and *O*-Alkylation of Ethyl *N*-Hydroxycarbamate (Hydroxyurethan)

Ethyl *N*-hydroxycarbamate may be alkylated to give *N*,*O*-dialkylhydroxylamines along with the *O*-alkylhydroxylamine [47–50a]. Fortunately, the separation of the two products is not difficult. The hydrogen which remains on the nitrogen atom in an O-substituted hydroxyurethan is sufficiently acidic that it can be separated readily from the *N*,*O*-dialkyl product by a caustic treatment (Eq. 26) [48]. Some special preparations [48–59] using this method are shown in Table I.



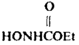
$$RX + HONHC(=O)OC_2H_5 \xrightarrow{KOH} RONHC(=O)OC_2H_5 \xrightarrow{(KOH)} \left[RON^{-}C(=O)OC_2H_5\right]K^{+} + H_2O \;(\text{soluble}) \xrightarrow{HX} RONH_2 + CO_2 + C_2H_5OH$$

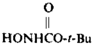
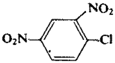
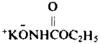
$$RONHC(=O)OC_2H_5 \xrightarrow{RX} RON(R)C(=O)OC_2H_5 \;(\textit{insoluble}) \xrightarrow{HX} RONHR + CO_2 + C_2H_5OH$$

(26)

### TABLE I

*N*- AND *O*-ALKYLATION OF ALKYL *N*-HYDROXYCARBAMATE[a]

| Carbamate (moles) | Alkylating agent (moles) | Solvent (ml) | Base (moles) | Reaction conditions |  | Product | Yield (%) | B.p., °C (mm Hg) or M.p., °C | Ref. |
|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  | Temp. (°C) | Time (hr) |  |  |  |  |
|  $HONHC(=O)OEt$<br>(2.0) | $(CH_3)_2SO_4$<br>(4.25) | $H_2O$<br>(960) | KOH<br>(4.25) | 25 | 2 | *N*-Methyl-*N*-methoxycarbamate | 30 | 150–155<br>(760) | 50a |
|  |  |  |  |  |  | ↓ $H_2O$<br>*N*,*O*-Dimethylhydroxylamine | — | 42–43 |  |
| (0.1) | $n\text{-}C_4H_9I$<br>(0.1) | $C_2H_5OH$<br>(30) | KOH<br>(0.1) | 80 | 5 | *N*-Ethyl-carboxyl *O*-butylhydroxylamine | 11.7 gm | — | 51 |
|  |  |  |  |  |  | ↓ KOH, $H_2O$<br>*O*-Butyl hydroxylamine | 41.7 | 156–157 |  |
| (1.52) | $CH_2{=}CH{-}CH_2Br$<br>(1.62) | $C_2H_5OH$<br>(330) | — | 80 | 2 | *N*-Ethylcarboxy-*O*-alkylhydroxylamine | 61<br>(12.5) | 107<br>(12.5) | 52 |
|  |  |  |  |  |  | ↓ 1. KOH, $H_2O$ 2. HCL<br>*O*-Allylhydroxylamine hydrochloride | 55 | 169–170 |  |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
|  $HONH\overset{\overset{O}{\|}}{C}O$-$t$-Bu<br>(0.1) | <br>(0.1) | $C_2H_5OH$<br>(200) | KOH<br>(0.1) | 25 | 1 | $t$-Butyl-$N$-(2,4-dinitrophenoxy)carbamate<br>↓ $CF_3COOH$ | 53 | 74–75 | 57 |
| | | | | | | $O$-(2,4-Dinitrophenyl)hydroxylamine | 50 | 112 | |
| (0.628) | $(C_6H_5)_2CHBr$<br>(0.435) | — | — | 80–85 | 4 | Ethyl-$N$-Benzhydryl-$N$-hydroxycarbamate<br>↓ NaOH, $H_2O$ | 40 | 114–117 | 59 |
| | | | | | | $N$-Benzhydrylhydroxylamine | | 78–80<br>(760) | |
|  $^{+}K\overset{-}{O}NH\overset{\overset{O}{\|}}{C}OC_2H_5$<br>(3.85) | $(C_6H_5)_2CHBr$<br>(2.6) | DMF<br>(2000) | $NaHCO_3$<br>(2.6) | 60 | 1–2 | Ethyl-$N$-benzyhydryloxycarbamate<br>↓ NaOH, $H_2O$ reflux 1 hr | 25.3 | 103–105 | 59 |
| | | | | | | $O$-Benzhydrylhydroxylamine | | 115–118<br>(0.4)<br>48 | |

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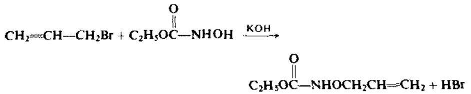
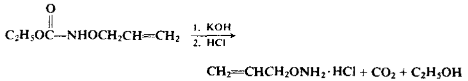
[a] Preparation 2-8 gives more details as to the usefulness of this method.

## *2-8. Preparation of O-Allylhydroxylamine Hydrochloride* [52a]



$$CH_2{=}CH{-}CH_2Br + C_2H_5O\overset{O}{\overset{\|}{C}}{-}NHOH \xrightarrow{KOH} C_2H_5O\overset{O}{\overset{\|}{C}}{-}NHOCH_2CH{=}CH_2 + HBr \quad (27)$$



$$C_2H_5O\overset{O}{\overset{\|}{C}}{-}NHOCH_2CH{=}CH_2 \xrightarrow[2.\ HCl]{1.\ KOH} CH_2{=}CHCH_2ONH_2 \cdot HCl + CO_2 + C_2H_5OH \quad (28)$$

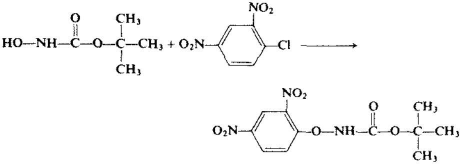
To a solution of 86.8 gm (1.55 moles) of potassium hydroxide in 330 ml of absolute ethanol is added a solution of 159 gm (1.52 moles) of ethyl *N*-hydroxycarbamate in 330 ml of absolute ethanol. With external cooling to maintain an internal temperature of 25°C to this mixture is added 195.5 gm (1.62 moles) of allyl bromide. After the addition has been completed, the mixture is heated under reflux for 2 hr. After separating the potassium bromide formed during the reaction and washing it with absolute alcohol, the alcoholic solution is evaporated under reduced pressure. The residue is dissolved in ether and then the ether solution is extracted repeatedly with 10% aqueous sodium hydroxide solution. [From the ether solution, on evaporation 25.5 gm (18%) of ethyl *N,O*-diallylhydroxycarbamate, b.p. 91–92°C (8.55 mm Hg) may be isolated.] The aqueous extract is acidified with 10% aqueous sulfuric acid and the ethyl *O*-allylhydroxycarbamate is extracted with ether. Upon evaporating the ether off, 134.2 gm (61%) of the intermediate product, b.p. 107°C (12.5 mm Hg), is isolated.

In a steam distillation apparatus, 134 gm of ethyl *O*-allylhydroxycarbamate is treated with a solution of 120 gm of potassium hydroxide in 280 ml of water. The product is steam-distilled into a receiver containing dilute hydrochloric acid.

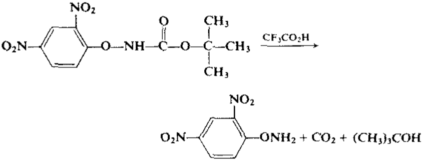
The steam distillate is evaporated under reduced pressure. The residue is taken up twice in absolute ethanol and dried by evaporation under reduced pressure. The yield is 91 gm (55%, overall), m.p. 169–170°C. Upon recrystallization from absolute alcohol and dry ether, the melting point is raised to 170.6–170.8°C (172–174°C [45]). Free *O*-allylhydroxylamine has the following reported properties: b.p. 98–99°C, $n_{\mathrm{d}}^{25}$ 1.4300 [52b].

The problems connected with the preparation of *O*-arylhydroxylamines by this method have been attributed to the instability of the aryl-substituted aminooxy group to the hydrolytic system used in its preparation. This problem has recently been circumvented by substituting for ethyl *N*-hydroxycarbamate, *t*-butyl *N*-hydroxycarbamate [57].

### *2-9. Preparation of O-(2,4-Dinitrophenyl)hydroxylamine* [57]



(29)

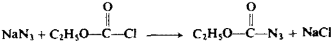


(30)

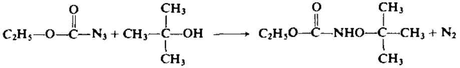
To a stirred solution of 13.3 gm (0.1 mole) of *t*-butyl *N*-hydroxycarbamate and 5.6 gm (0.1 mole) of potassium hydroxide in 200 ml of absolute ethanol is added 20.2 gm (0.1 mole) of 2,4-dinitrochlorobenzene. The resultant deep red solution is stirred at room temperature for 1 hr; then enough glacial acetic acid is added dropwise to produce a light yellow solution. The solution is poured into 1.5 liters of cold water. The yellow oil which separates is gradually converted to crystals. The solid *t*-butyl *N*-(2,4-dinitrophenoxy)carbamate is separated, dried, and recrystallized from an ethyl acetate-hexane mixture to afford 16.4 gm (53%), m.p. 74–75°C. To 15 ml of trifluoroacetic acid is added 4 gm (0.0133 mole) of the *t*-butyl *N*-(2,4-dinitrophenoxy)carbamate. After the evolution of carbon dioxide has subsided, the solution is poured into 100 ml of ice water. The resultant oily layer crystallizes on standing to afford 2.5 gm (95%), m.p. 112°C (from ethanol).

Recently it was discovered that the alkylation of ethyl *N*-hydroxycarbamate under alkaline conditions, particularly in a DMF medium at 60°C in the presence of sodium bicarbonate, leads to the ultimate formation of *O*-alkylated hydroxylamines. On the other hand, at 80–85°C, the direct alkylation without the presence of a base ultimately leads to *N*-alkylhydroxylamines (see Table I) [59].

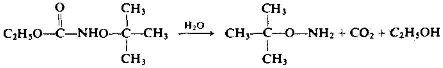
The reaction of ethylazidoformate with an alcohol, while perhaps hazardous, may have some merit (Eqs. 31–33). The overall yield, based on ethyl chloroformate, is said to be on the order of 60% [38c].



$$NaN_3 + C_2H_5O{-}\overset{\overset{O}{\|}}{C}{-}Cl \longrightarrow C_2H_5O{-}\overset{\overset{O}{\|}}{C}{-}N_3 + NaCl \tag{31}$$



$$C_2H_5{-}O{-}\overset{\overset{O}{\|}}{C}{-}N_3 + CH_3{-}\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}{-}OH \longrightarrow C_2H_5O{-}\overset{\overset{O}{\|}}{C}{-}NHO{-}\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}{-}CH_3 + N_2 \tag{32}$$



$$C_2H_5O{-}\overset{\overset{O}{\|}}{C}{-}NHO{-}\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}{-}CH_3 \xrightarrow{H_2O} CH_3{-}\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}{-}O{-}NH_2 + CO_2 + C_2H_5OH \tag{33}$$

### G. *O*-Alkylation of *N*-Hydroxyphthalimide

The Ing-Manske modification of the Gabriel synthesis of primary amines is well known.

An analogous reaction has been developed in which *N*-hydroxyphthalimide is *O*-alkylated. The product of the reaction is then hydrolyzed or hydrazinolyzed to produce *O*-alkylhydroxylamines. The early examples of this alkylation of *N*-hydroxyphthalimide were carried out under the erroneous belief that the starting material was phthaloxime [41, 42a]. More recently the structure of this compound has been determined by infrared spectroscopy and other means to be *N*-hydroxyphthalimide [42b, 60]. Although the structure of this compound was not accurately known, it had been used as early as 1928 to prepare *O*-methylhydroxylamine [42a]. More recently it has become the starting compound of one of the standard procedures for the preparation of a range of O-substituted hydroxylamines [42c].

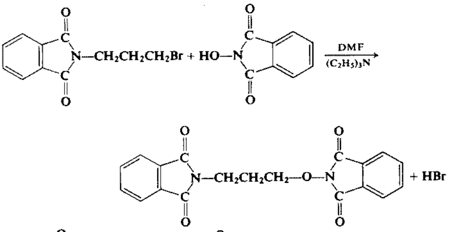
The alkylation of *N*-hydroxyphthalimide has been carried out in a variety of solvents. Its silver salt has been alkylated in ether [41, 42b]. In the presence of various bases, alkylations have been carried out in water [60], methanol [42a], dimethylformamide [35b, 42c, 46, 61–63], acetone [64, 65], and dimethyl sulfoxide [66].

The synthesis in an aqueous medium is quite straightforward but has been confined to reactions involving the lower alkyl halides or dialkyl sulfates [60]. By this means, *O*-methylhydroxylamine hydrochloride (m.p. 150–151°C) and *O*-ethylhydroxylamine hydrochloride (m.p. 129–131°C) have been prepared.

The methods carried out in dimethylformamide (DMF) and dimethyl sulfoxide appear to have wider applicability. On working up the reaction medium, the typical procedure calls for diluting the DMF or DMSO solutions with water. In the example cited here, recovery of the products seems to be quite good. However, if these procedures are to be extended to new examples, this step must be carefully investigated since it is quite possible that solutions of the order of 25% DMF or DMSO in water may still be solvents for appreciable quantities of the product.

Preparation 2-8 is not only typical of the use of DMF as a solvent, it is a preparation of a primary amine and of an O-substituted hydroxylamine by two simultaneous Ing-Manske reactions.

### *2-10. Preparation of* **O-(3-Aminopropyl)hydroxylamine** *(3-Aminopropyloxyamine) (in DMF System)* **[35b]**



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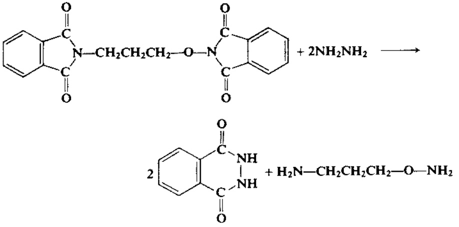


(36)

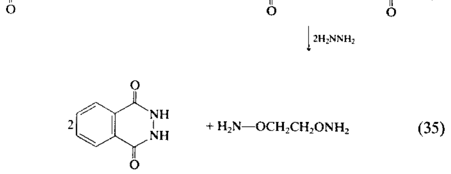
Over a 1-hr period, the temperature of a stirred solution of 150 gm (0.56 mole) of γ-bromopropylphthalimide, 91.7 gm (0.56 mole) of *N*-hydroxyphthalimide, 121 gm (1.2 moles) of triethylamine, and 700 ml of dimethyl formamide (DMF) is raised gradually to 90°C. The reaction mixture is cooled to room temperature and poured into 2 liters of water. The precipitate is collected (176 gm, 89.3%; m.p. 177–179°C). Upon recrystallization (two times from glacial acetic acid, 8ml/gm), the melting point is raised to 178–180°C.

To a solution of 35.0 gm (0.1 mole) of 3-*N*-phthalimidopropyloxy-*N*-phthalimide in 200 ml of DMF maintained at 70°C is added 20 gm (0.4 mole) of hydrazine hydrate. After allowing the solution to cool to room temperature over a 1-hr period, 300 ml of cold water is added and the pH of the solution is adjusted to pH 3 with hydrochloric acid. The precipitated phthalhydrazide is separated by filtration; the filtrate is evaporated between 40 and 50°C under reduced pressure. The residue is dissolved in 1 liter of methanol and the resulting solution is passed through a column containing 1 liter of IRA-400 ion-exchange resin (in $OH^-$ form, and previously treated with methanol). After the eluant is collected the column is rinsed with 1.5 liters of methanol. The eluant and methanol rinsings are combined and concentrated under reduced pressure to afford 3.0 gm (45%), b.p. 110–115°C/3 mm Hg. On redistillation 2 gm (30%) of purified product is isolated; b.p. 99°C/40 mm Hg; $n_D^{25}$ 1.4615; $d_4^{25}$ 0.999.

NOTE: The reported reduction in boiling point on redistillation is unusual and should be rechecked.

Dihydrochloride salt, m.p. 208–209°C (dec.).

***2-11. Preparation of 1,2-Bis(aminooxy)ethane* [35c]**



(35)

1,2-Bis(phthalimidooxy)ethane is prepared according to a modified procedure of Bauer and Suresh [35d], in which 1 equiv. of 1,2-dibromoethane is alkylated with 2 equiv. of *N*-hydroxyphthalimide in DMF containing 6 equiv. of trimethylamine, to give an 84% yield of the desired product in the form of white needles. The white solid is recrystallized from hot DMF (this step is not essential because the crude product can be used in the next step of this preparation m.p. 248–249°C. (lit. [35d] m.p. 254°C.)

To 20.0 g (0.0568 mole) of 1,2-bis(phthalimidioxy)ethane in 120 ml 95% ethanol at room temperature, while stirring, is added 5.81 ml of 95% hydrazine (0.174 mole) dropwise via a syringe over a 10-min period while nitrogen is kept over the reaction mixture. The reaction is mildly exothermic, and 5 min after the addition is complete, phthalhydrazide precipitated from the solution. The white precipitate is broken up and the mixture stirred for 2 hr, 50 ml 95% ethanol added, and filtered, and the phthalhydrazide is washed with 95% ethanol. The filtrates combined, and the solvent is removed under reduced pressure. Then 100 ml of methylene is added to the residue, and after storing at 10°C for 24 hr, the precipitated phthalhydrazide is filtered. The filtrate is dried ($MgSO_4$), and the solvent is removed under reduced pressure to give 3.39 g of a colorless liquid (65% yield).

IR ($CHCl_3$): 3325, 3000, 2925, 1585, 1188, 1050 $cm^{-1}$; $H^1$ NMR ($CDCl_3$) $\delta$ 3.71 (*s*, 4H), 5.31 (*s*, 4H exchange with $D_2O$);$C^{13}$NMR ($CDCl_3$) $\delta$ 73.7; mass spectrum, *M*/*e* (relative intensity) 93 ($M^+ + H$, 100), 92 (M, 20, 66 (59), 65 (23), 64 (10), 63 (13).

The dihydrobromide salt has been previously reported by Bauer and Suresh.

### H. *O*-Alkylation of Benzohydroxamic Acid

Another method of blocking the amino position of hydroxylamine involves the use of hydroxamic acids such as benzohydroxamic acid. Use of this reagent to prepare *O*-alkylbenzohydroxamic acid, followed by hydrolysis, has long been considered a reasonable method of preparing *O*-alkylhydroxylamines [67–73].

The chemistry of hydroxamic acid is discussed in greater detail in Chapter 12. Suffice it to state here that while monoalkylation of potassium benzohydroxamate predominantly produces *O*-alkyl derivatives, because of the tautomerism of the molecule, dialkylation may lead to complex mixtures of products [67].

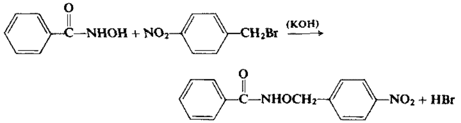
Traditionally, the potassium or sodium salts of benzohydroxamic acid are alkylated, sometimes in the presence of potassium bicarbonate. It has been observed that under these conditions some N-alkylation may take place [68].

More recently, benzohydroximate derivatives, i.e., compounds in which both oxygens are alkylated, have also been detected. There are some indications that simple *O*-alkylation of benzohydroxamic acid tends to predominate as the chain length of the alkylating agent increases [67].

The effect of the acidity of the reaction medium should be investigated in relation to the alkylation of the hydroxamic acids. It may be that by such control of the acidity of the reaction medium, the distribution of the products may be modified materially.

One other factor to be considered is the possibility of product losses by the Lossen rearrangement [45].

### 2-12. *Preparation of* O-(p-*Nitrobenzyl)hydroxylamine Hydrochloride* [69]



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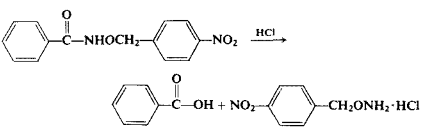


(38)

To a solution of 25 gm (0.183 mole) of benzohydroxamic acid in 28 ml of ethanol and 10.2 gm (0.184 mole) of potassium hydroxide in 40 ml of water is added a hot solution of 39.4 gm (0.184 mole) of *p*-nitrobenzyl bromide in ethanol. The mixture is then heated under a reflux condenser for 45 min and cooled. The precipitated crystals are separated and crystallized from ethanol. (No yield reported.)

A solution of 15 gm (0.055 mole) of the above *O*-*p*-nitrobenzylbenzohydroxamic acid (*p*-nitrobenzyl benzohydroxamate) in 125 ml of hot ethanol is heated to reflux for 25 min with 150 ml of conc. hydrochloric acid.

To prevent the precipitation of the final product during the work-up, the following steps are carried out rapidly.

The clear solution is diluted with 150 ml of water and while still warm benzoic acid and other by-products are separated by extraction with 200 ml of chloroform. The aqueous layer is evaporated to dryness under reduced pressure to afford a crude yield of 10.75 gm (96%). The residue is recrystallized from hot 2 *N* hydrochloric acid and washed in turn with ethanol and with ether to afford a solid, m.p. 217°C.

The free base may be produced by neutralizing the salt with sodium carbonate solution; *O*-*p*-nitrobenzylhydroxylamine, m.p. 56°C (recrystallized from petroleum ether).

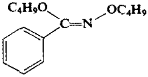
By a similar technique, *O*-allylhydroxylamine hydrochloride, m.p. 172°C (dec.) was also prepared [70].

An examination of the product of butylating benzohydroxamic acid showed that a nonacidic fraction and an equal weight of an acidic fraction were readily isolated.

The nonacidic fraction contained mainly *O*,*O*′-dibutyl benzohydroximate (b.p. 175–180°C/13 mm Hg) and some aniline (probably formed during the reaction by a Lossen rearrangement). On hydrolysis with ethanolic hydrochloric acid, the hydroximate produced ethyl benzoate and *O*-butylhydroxylamine hydrobromide (m.p. 159–161°C; hydrochloride, m.p. 156–157°C) [51].

The acidic fraction contained mainly *O*-butylbenzohydroxamic acid (butyl benzohydroxamate) which on hydrolysis formed *O*-butylhydroxylamine hydrochloride and benzoic acid [51]. It has been contended that in this particular work, the presence of an *N*,*O*-dibutylbenzohydroxamic acid had been overlooked [67]. The major source of *O*-butylhydroxylamine hydrochloride is from the acidic fraction, although the yield is not particularly high.

The initial preparation of the butylated benzohydroxamic acid derivatives has been repeated recently [67]. The analysis of the reaction products by vapor-phase chromatography showed it to contain 43% of *O*-butylbenzohydroxamic acid (butyl benzohydroxamate), 17% of *N*,*O*-dibutylbenzohydroxamic acid, and 8% of *n*-butyl(Z)-*O*-*n*-butylbenzohydroximate:

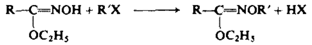


The nature of the remaining 32% of the crude reaction product was not determined.

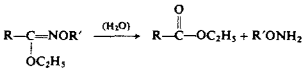
The use of benzohydroxamic acid has been extended to the preparation of a variety of O-substituted hydroxylamines. For example, halocarboxylic acids have been used as alkylating agents to produce α-aminooxy acids of the type, $NH_2O(CH_2)_nCO_2H$ [71]. A variety of *O*-benzylhydroxylamines [68], *O*-aralkylhydroxylamines [46], as well as simpler O-substituted hydroxylamines [72] have also been prepared. In some of these preparations, the hydrolysis of the O-substituted benzohydroxamic acid was carried out with hot alcoholic hydrogen chloride. This treatment evidently prevented the O-N cleavage which had been observed during the aqueous hydrolysis of the substituted benzohydroxamic acids [46].

### 1. *O*-Alkylation of Ethyl Acetohydroximate

Nearly a century ago there were reports of the preparation of alkylated hydroximic acids which could be hydrolyzed to *O*-substituted hydroxylamines (Eqs. 39 and 40) [74, 75].



$$\mathrm{R{-}\underset{\substack{|\\ OC_2H_5}}{C}{=}NOH + R'X \longrightarrow R{-}\underset{\substack{|\\ OC_2H_5}}{C}{=}NOR' + HX} \tag{39}$$

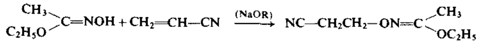


$$\mathrm{R{-}\underset{\substack{|\\ OC_2H_5}}{C}{=}NOR' \xrightarrow{(H_2O)} R{-}\overset{\substack{O\\ \|}}{C}{-}OC_2H_5 + R'ONH_2} \tag{40}$$

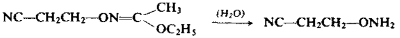
The reaction formally resembles the preparation of such derivatives by the O-alkylation of oximes. However, the question of the structure of the hydroximate esters was not settled in the early work and even if that research had been correctly interpreted in the light of current structural theories, the possibility of such a method of synthesis received no further attention until recently.

In 1961, this method of preparing *O*-alkylhydroxylamines was presented as a novel, particularly effective synthesis [76]. Other methods of preparing such compounds were criticized because it was thought that wide variations in reaction conditions were required with different alkylating agents and because the hydrolytic conditions were considered to severe to permit preparation of more complex compounds. Yet, present experience indicates that the use of esters of hydroximic acid may indeed be a reasonable alternate method of preparing *O*-alkylhydroxylamines. Revival of interest in the hydroximates is further justified because they will react under Michael conditions to produce hydroxylamine derivatives according to Eqs. 41 and 42.

Problems with the use of ethyl acetohydroximate arise from the question of availability of this reagent compared with the accessibility of ethyl *N*-hydroxycarbamate, of benzohydroximate acid, or of oximes and from



$$\left.{}^{\mathrm{CH_3}}_{\mathrm{C_2H_5O}}\right>\mathrm{C{=}NOH} + \mathrm{CH_2{=}CH{-}CN} \xrightarrow{(\mathrm{NaOR})} \mathrm{NC{-}CH_2CH_2{-}ON{=}C}\left<{}^{\mathrm{CH_3}}_{\mathrm{OC_2H_5}}\right. \qquad (41)$$



$$\mathrm{NC{-}CH_2CH_2{-}ON{=}C}\left<{}^{\mathrm{CH_3}}_{\mathrm{OC_2H_5}}\right. \xrightarrow{(H_2O)} \mathrm{NC{-}CH_2CH_2{-}ONH_2} \qquad (42)$$

the question of whether (*Z*)- and (*E*)-isomers are equally readily alkylated and hydrolyzed.

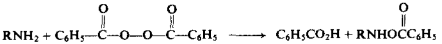
### *J. Benzoyloxylation of Amines*

Dibenzoyl peroxide has been used to benzoyloxylate primary and secondary aliphatic amines [77–78b] However, not only must the usual precautions in handling dry benzoyl peroxide be observed; this reagent is also warmed in the medium, with attendant hazards; and, if ether is used as a solvent, the hazardous ether hydroperoxides may form.

**CAUTION:** In view of its even greater hazards, acetyl peroxide must, of course, not be used in this reaction. Furthermore, aromatic amines must not be used as the co-reactants, since explosive reactions between aromatic amines and dibenzoyl peroxide are known to be common. Aralkylamines such as dibenzylamine, have, however, been used in the reaction.

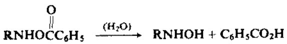
In any case, only small-scale preparations should be attempted in a secure hood.

The first step in the reaction is the formation of an N- or N,N-substituted *O*-benzoylhydroxylamine (Eq. 43).



$$\mathrm{RNH_2} + \mathrm{C_6H_5{-}\overset{\overset{O}{\|}}{C}{-}O{-}O{-}\overset{\overset{O}{\|}}{C}{-}C_6H_5} \longrightarrow \mathrm{C_6H_5CO_2H} + \mathrm{RNHO\overset{\overset{O}{\|}}{C}C_6H_5} \qquad (43)$$

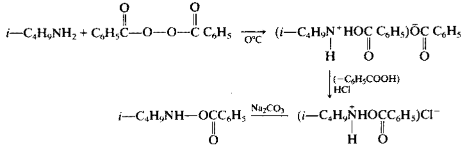
Hydrolysis of the *O*-benzoylhydroxylamine produces the substituted hydroxylamine (Eq. 44).



$$\mathrm{RNHO\overset{\overset{O}{\|}}{C}C_6H_5} \xrightarrow{(\mathrm{H_2O})} \mathrm{RNHOH} + \mathrm{C_6H_5CO_2H} \qquad (44)$$

By appropriate selection of the aliphatic amine, a wide variety of *N*-alkyl-and *N,N*-dialkylhydroxylamines may be prepared. However, these reactions may not be generally safe and great care should be exercised in attempting to follow any of the reported procedures.

### 2-13. *Preparation of* N*-Isobutyl-O-benzoylhydroxylamine* [78c]



$$i\text{—}C_4H_9NH_2 + C_6H_5\overset{\overset{O}{\|}}{C}\text{—}O\text{—}O\text{—}\overset{\overset{O}{\|}}{C}\,C_6H_5 \xrightarrow[0^\circ C]{} (i\text{—}C_4H_9\underset{H}{\underset{|}{N^+}}HO\underset{\underset{O}{\|}}{C}\,C_6H_5)\bar{O}\underset{\underset{O}{\|}}{C}\,C_6H_5$$

$$\Big\downarrow{\scriptstyle (-C_6H_5COOH) \atop HCl}$$

$$i\text{—}C_4H_9NH\text{—}O\underset{\underset{O}{\|}}{C}C_6H_5 \xleftarrow{Na_2CO_3} (i\text{—}C_4H_9\underset{H}{\underset{|}{\overset{+}{N}}}HO\underset{\underset{O}{\|}}{C}C_6H_5)Cl^- \qquad (45)$$

Following the method reported by Zinner [78c] to 29.2 g (0.4 mole) of isobutylamine dissolved in 40 ml benzene (suggest toluene instead) is added a solution of 48.4 g (0.2 mole) of dibenzoyl peroxide in 200 ml benzene (suggest toluene instead), with stirring and cooling to 0°C. The yellow-colored reaction was first heated for 30 min at 30°C and then 30 min at 50°C. After cooling to 0° *N*-isobutylammonium benzoate separates as a white precipitate. The filtrate is washed with water and dried over magnesium sulfate. The mixture is filtered, and then anhydrous hydrogen chloride is bubbled through the solution to give 12.1 g (26% yield) of a white precipitate of *N*-isobutyl-*O*-benzoylhydroxylamine hydrochloride, m.p. 120–128°C. The infrared spectrum in Nujol indicated an absorbtion band at 1760 $cm^{-1}$.

Treatment of the latter product with 1N aqueous sodium carbonate and then extraction with ether, drying over sodium sulfate and evaporation gave *N*-isobutyl-*O*-benzoylhydroxylamine. Precipitation of the latter by Kugelrohr distillation gave product b.p. 58–65°C (0.04–0.03 mm Hg). The IR ($CCl_4$) indicated 3235, 1725, 1267, 1088, 1067, 1027 $cm^{-1}$; and the NMR ($CCl_4$) indicated $\delta$, 0.99(*d*, $J = 6.5$ Hz. 6H), 1.83 (*m*, $J = 6.5$ Hz, 1H), 2.87 (*d*, $J = 6.5$ Hz, 2H), 7.47 and 7.98 (aromatic m and NH).

## K. Reactions of Grignard Reagents

A variety of nitrogen-containing compounds have been treated with Grignard reagents in an effort to produce substituted hydroxylamines [79–95]. Many of these reactions have not been explored extensively and no reasoned judgement as to general applicability can be made. These methods were presented in outline form in Schemes 2 and 3.

## L. Reaction of Chloramine with Alcoholates

The reaction of chloramine and an alcoholate according to Eq. (46) appears attractive since it involves the direct formation of the oxygen-to-nitrogen bond in an *O*-alkylated hydroxylamine [92–95].

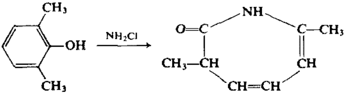
$$R{-}O^-Na^+ + ClNH_2 \longrightarrow RONH_2 + NaCl \qquad (46)$$

One series of experiments, carried out in benzene solution at 0°C, involving the reaction of sodium 2-phenoxyethanol with chloramine resulted in the production of *O*-(2-phenoxyethyl)hydroxylamine hydrochloride [m.p. 172–174°C (dec.)] in very low yields [91]. From benzyl alcohol, *O*-benzylhydroxylamine hydrochloride (m.p. 229–235°C) was prepared. However, this reaction failed with other alcohols.

On reexamination of the procedure, it was found that when a solution of chloramine was added to a true solution of the sodium alcoholate in an alcohol or in an alcohol/dioxane mixture at room temperature or higher, reasonable quantities of a wide variety of *O*-alkylhydroxylamines could be prepared [92]. The validity of these observations was confirmed by other investigators although yields were not always considered reproducible [45, 46].

The discussion in this chapter up to this point has indicated that a variety of methods for the preparation of *O*-alkyl and *O*-aralkyl hydroxylamines have been developed. However, *O*-arylhydroxylamines are virtually unknown [36]. This new method seemed to be a natural approach to the preparation of such compounds by the reaction of phenolates with chloramine.

Therefore a series of 2,6-disubstituted phenolates were reacted in molten phenols as solvent. The resultant products were isolated and thought to be the desired aromatic hydroxylamines [93a]. However, on further examination of these products, it was found that the reaction of 2,6-dimethylphenol produced a dihydroazepinone according to Eq. (47) and not the *O*-arylhydroxylamine [93b,c, 94].



(47)

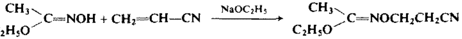
## 3. ADDITION REACTIONS

### A. Addition of Hydroxylamine and Related Compounds to Activated Olefins

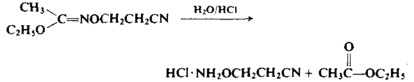
With certain activated olefinic compounds, hydroxylamine and substituted hydroxylamines undergo addition reactions which resemble Michael addition reactions [96–104]. The exact course of the reaction, and consequently, the nature of the reaction products are not always predictable.

The nature of the activating groups conjugated with the olefinic bond, the substituents on the hydroxylamine, catalysts, and reaction medium affect the structure of the final product. Naturally, the fact that hydroxylamine has one hydrogen bonded to an oxygen atom and two hydrogens bonded to the nitrogen atom, in effect, makes it trifunctional, thus adding to the complexity of the reaction. The reaction is summarized in Scheme 4 and Preparation 3-1 is a typical one.

***3-1. Preparation of β-Aminohydroxypropionitrile Hydrochloride* [76]**



$$\mathrm{(CH_3)(C_2H_5O)C{=}NOH + CH_2{=}CH{-}CN \xrightarrow{NaOC_2H_5} (CH_3)(C_2H_5O)C{=}NOCH_2CH_2CN} \tag{48}$$



$$\mathrm{(CH_3)(C_2H_5O)C{=}NOCH_2CH_2CN \xrightarrow{H_2O/HCl} HCl\cdot NH_2OCH_2CH_2CN + CH_3\overset{\displaystyle O}{\overset{\|}{C}}{-}OC_2H_5} \tag{49}$$

To a solution of 22 gm (0.2 mole) of ethyl acetohydroximate in anhydrous dioxane is added 13.6 gm (0.2 mole) of sodium ethoxide. To this mixture is added, with vigorous stirring, 12 gm (0.2 mole) of acrylonitrile. Stirring is continued at 30°C for 48 hr. Then the reaction mixture is neutralized with alcoholic hydrogen chloride and filtered. The filtrate is fractionally distilled. The fraction boiling between 78° and 81°C/3 mm Hg is retained as the intermediate product; yield, 14 gm (50%). To this cyanoethylated product is added a calculated amount of water and hydrogen chloride. From this mixture 10.2 gm (82%) of β-aminohydroxypropionitrile hydrochloride is isolated, m.p. 131°C.

## B. Methods for Preparation of α-Hydroxylaminonitriles

The α-hydroxylaminonitriles are of interest because of their relation to the hydroxylamino acids. The methods for the preparation usually involve the addition of hydrogen cyanide to oximes or precursors of these compounds.

Thus, there are essentially four variations:

1. Reaction of oximes with anhydrous hydrogen cyanide under various reaction conditions.

2. Reaction of an aldehyde or ketone with a hydroxylamine salt and sodium cyanide—a variation of the Strecker synthesis. This method is satisfactory for reactions involving many ketones such as acetone or cyclopentanone, but not with acetophenone, benzaldehyde, phenylacetaldehyde, and hydrocinnamaldehyde.

3. Reaction of oximes, particularly aldoximes, with sodium cyanide and sodium bisulfite. This method, while satisfactory for many preparations, also fails for oximes of benzaldehyde and hydrocinnamaldehyde [105].

4. Reaction of oximes with sodium cyanide in a phosphate buffer which maintains the reaction at pH 7 [106–110].

In all of these preparations, all due precautions for reactions involving hydrogen cyanide or sodium cyanide must be taken.

## 4. OXIDATION REACTIONS

Substituted hydroxylamines can also be prepared by the oxidation of the corresponding primary and secondary amines. However, because the *N*-substituted hydroxylamines are reducing agents, one may anticipate that difficulties will be experienced in such preparations [111–114].

$$R_2NH \xrightarrow{(O)} R_2NOH \qquad (50)$$

Related is the oxidation of tertiary amines, to give the amine oxides, which on thermal decomposition give the hydroxylamine (see Section 6).

### A. Oxidation of Secondary Amines

Some secondary amines have been oxidized to produce various quantities of *N*,*N*-disubstituted hydroxylamines. For example, *N*-hydroxymorpholine is produced in 5.4% yield [111a]. In other cases, yields in the range of 20–50% have been reported. Therefore the oxidation of secondary amines is only a fair method of preparation [111b,c,d,e,f].

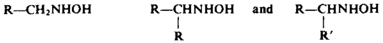
### B. Oxidation of Anilinomagnesium Bromide

Mention has already been made that anilinomagnesium bromide has been oxidized to *N*-phenylhydroxylamine (m.p. 81–82°C). This reaction appears to have been neglected. Whether this reaction [79] is of preparative value is yet to be ascertained.

## 5. REDUCTION REACTIONS

### A. Reduction of Oximes

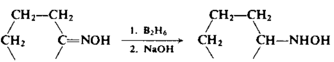
Considering the ready availability of a wide variety of oximes, the reduction of such compounds to the substituted hydroxylamines represents a synthetic procedure which permits the preparation of a wide variety of structural types. Of course, such a procedure only permits the preparation of N-substituted hydroxylamines of the following structures:



$$R{-}CH_2NHOH \qquad \underset{R}{R{-}CHNHOH} \quad \text{and} \quad \underset{R'}{R{-}CHNHOH}$$

While a number of attempts have been made to hydrogenate oximes [115–121], this approach has not been very fruitful. The reduction with diborane, on the other hand, appears to be a very general method of synthesis of N-substituted hydroxylamines [115–117]. Its main shortcoming is that it should only be diborane. Care should also be observed since diborane reduces oximes and hydroxylamines at 105–110°C to amines [117].

### *5-1. Preparation of* N*-Cyclohexylhydroxylamine* [116]



(51)

In a three-necked, 50 ml flask equipped with a magnetic stirrer, thermometer, condenser with provision for the venting of hydrogen, and a serum cap, and containing 2.26 gm (0.02 mole) of cyclohexanone oxime at 0°C is added by means of a hypodermic syringe 17 ml of a 2 *M* solution of diborane in tetrahydrofuran at such a rate that the reaction temperature is always maintained below 10°C. After the addition has been completed, the reaction is continued for 4 hr at room temperature. Then the solvent is removed under reduced pressure and the flask's content is cooled to 0°C. By means of a syringe a few drops of 10% aqueous sodium hydroxide is added slowly.

**CAUTION:** Considerable heat may evolve at this point. In one case, a mild explosion has been reported.

Then a total of 10 ml of 10% aqueous sodium hydroxide is added. The reaction mixture is then refluxed for 1 hr and the product is separated from the reaction mixture by a 90 hr continuous extraction with pentane. The pentane solution is evaporated in a nitrogen stream to give a crude residue which sublimes at 60°C/1 mm Hg to afford 1.89 gm (82%), m.p. 140°C.

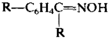
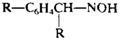
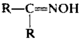
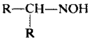
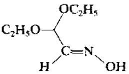
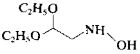
A few methods from the recent literature are shown in Table II.

## B. Reduction of Nitrones

Several nitrones have been reduced with lithium aluminum hydride to produce N,N-disubstituted hydroxylamines. The reaction is probably quite

TABLE II

REDUCTION OF OXIMES TO HYDROXYLAMINES

| Oxime | Reducing agent | Product | Ref. |
|---|---|---|---|
|  $R{-}C_6H_4C(R){=}NOH$ | Pyridine-borane (via Pyr · HCl $NaBH_4$) |  $R{-}C_6H_4CH(R){-}NOH$ | *a* |
| or | | or | |
|  $R{-}C(R){=}NOH$<br>(alkyl type) | |  $R{-}CH(R){-}NOH$ | *b* |
| $CH_3CH{=}NOH$ | Pd/C + $H_2$ + NaOH | $(C_2H_5)_2NOH$[d] | |
|  | $Na(BH_3CN)/(CH_3COOH)$ 0°C |  | *c* |

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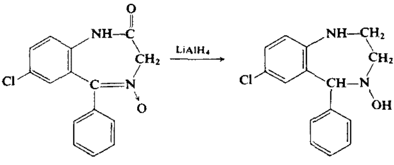
[a] Y. Kikugawa and M. Kawase, *Chem. Lett.* (11) 1279 (1977); *Chem. Abstr.* **88,** 37371q (1978). [b] Ube Industries Ltd., Jpn. Kokai Tokkyo Koho JP 82 88,153 June 1, 1982; *Chem. Abstr.* **97,** 181709j (1982). [c] E. Gehrer, W. Klotzer, N. Singewald and J. Stad/Wieser, *J. Chem. Soc. Communications* **633** (July, 1987). [d] This is an unusual product because one would have expected $CH_3CH_2NHOH$.

general, as illustrated by the reduction of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one-4-oxide to 7-chloro-4-hydroxyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (m.p. 170°–172°C) (Eq. 52) [118].



(52)

While the reduction of nitrones is an attractive method for the preparation of N,N-disubstituted hydroxylamines, its obvious shortcoming is the inaccessibility of nitrones.

## C. Reduction of *C*-Nitroso Compounds

Like the reduction of nitrones, the reduction of *C*-nitroso compounds as a method of producing N-substituted hydroxylamines suffers from the lack of a variety of starting materials. Furthermore, the *C*-nitroso compounds which may be available are primarily aromatic compounds. A limitation of the use of *C*-nitroso compounds as a source of hydroxylamines consists of the fact, which we have discussed elsewhere in this series, that *C*-nitroso compounds condense with hydroxylamines, particularly hydroxylamines produced by such a reduction, to afford azoxy compounds.

However, Bamberger reported the reduction of nitrosobenzene with zinc dust and sulfuric acid, or with zinc dust and water in 1894 [122]. A more recent example has been reported [123a]

A report in the literature describes the reduction of $(Me_3C)_2NO$ by $PhNHNH_2$ in methanol (violent elimination of $N_2$ reported) to give $(Me_3C)_2NHOH$, m.p. 65–66°C [123b].

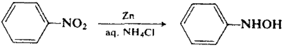
## D. Reduction of Nitro Compounds

The reduction of aromatic nitro compounds is one of the earliest methods of producing *N*-arylhydroxylamines [122–140a,b]. While a variety of reducing agents has been used, zinc dust and water or zinc dust and aqueous ammonium chloride are perhaps the most common reducing systems proposed. The preferred system avoids strong alkalis or mineral acids since alkalis decompose phenylhydroxylamines at room temperature and mineral acids cause their rearrangement to *p*-aminophenol. This reduction method is also effective for aliphatic nitro compounds [140c].

Attention to details of the reaction conditions are important in the case of the zinc dust–water reduction. For example, reduction was successful with a grade of zinc dust which analyzed 66.9% zinc, while a grade containing 67.3% zinc produced only aniline from nitrobenzene. Consequently the grade of zinc must be pretested; the ratio of reagents, the reaction time, and the intensity of the heating cycle must all be ascertained [124].

In Preparation 5-2 it is important that all of the steps from beginning to end follow each other in rapid succession.

### *5-2. Preparation of* N-*Phenylhydroxylamine* [18]



(53)

To a dispersion of 180 gm (2.75 gm-atom) of zinc dust in 500 ml of 50% aqueous ethanol, with vigorous stirring, is added 130 ml (156 gm, 1.27 mole) of nitrobenzene. The reaction is initiated by the dropwise addition of an aqueous ammonium chloride solution and can thereafter be maintained at a controllable rate by the cautious addition of the remaining ammonium chloride solution. The reaction temperature rises during this reduction step. Once reflux has subsided, the basic zinc salts are filtered off using a sintered glass funnel. The light green filtrate is cooled in an ice-salt mixture to precipitate the product. The yield is 100 gm (72.2%), m.p. 81°C.

The reduction of 2-methyl-2-nitropropane is carried out in a similar manner at 10–20°C to afford a 68% yield of *N*-*t*-butylhydroxylamine (m.p. 60–62°C) [140b].

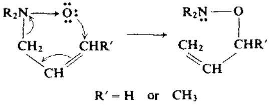
More recent methods for the reduction of nitro compounds are shown in Table III, along with the references to each.

### E. Reduction of Cyclic Imide Derivatives

*N*-Hydroxysuccinimide and *N*-methoxysuccinimide have been reduced with lithium aluminum hydride to produce *N*-hydroxypyrrolidine and *N*-methoxypyrrolidine [137].

## 6. REARRANGEMENT AND THERMAL DEGRADATION REACTIONS OF TERTIARY AMINE OXIDES AND RELATED COMPOUNDS*

The rearrangement reactions which produce *N*,*N*,*O*-trialkylhydroxylamines are confined to those tertiary amine oxides which bear at least one allyl, benzyl, or crotyl group on the nitrogen atom [62, 138–140]. The rearrangement reaction may be carried out in the presence of aqueous sodium hydroxide if the amine oxide does not form hydrates (e.g., allylmethylaniline oxide), otherwise the rearrangement is carried out thermally (e.g., in the case of *N*,*N*-dialkyl-*N*-allylamine oxides [140–148]. The reaction has been reviewed briefly in Cope and Towle [52a]. The mechanism of the rearrangement has been represented as follows [52a]:



$R' = H$ or $CH_3$ (54)

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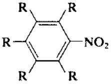
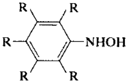
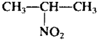
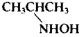
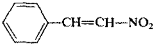
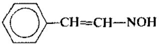
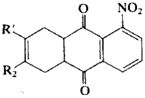
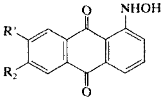
*See Schemes 5 and 6.

TABLE III

THE REDUCTION OF NITROCOMPOUNDS TO GIVE HYDROXYLAMINES

| Nitro compound | Reducing agent | Product | Ref. |
|---|---|---|---|
| $RNO_2$<br>where ($R{=}CH_3$, Et, *n*-Pr, iso-Pr.) | $H_2$/Pd oxide in $CH_3OH$ | RNHOH | *a* |
| $CH_3NO_2$ | $H_2$/Pd—C in $CH_3OH$ in $H_2SO_4$ | $CH_3NHOH$ | *b* |
| $CH_3NO_2$ | $H_2$/Pt—C in 3.5N $H_2SO_4$ containing S | $CH_3NHOH$ | *c* |
|  | $H_2$/Pt—C + $R_2NH$ or $R_3N$ |  | *d* |
|  $CH_3{-}\underset{\displaystyle NO_2}{\underset{\vert}{CH}}{-}CH_3$ | Undivided Flooded Bipolar Electrolytic Cell |  $CH_3\underset{\displaystyle NHOH}{CH}CH_3$ | *e* |
| $C_2H_5NO_2$ | $H_2$/Pd, Rh and 44% Rh—Pd using controllable electrical potential of 0.5 V | $C_2H_5$—NHOH | *f* |
| $RNO_2$<br>where R=alkyl or aryl | $H_2$/Pt—Nitrogen base<br>Phosphorous Compound | RNHOH | *g* |

| | | | |
|---|---|---|---|
|  | $BH_3 \cdot$THF Cat. amount $NaBH_4$ |  | *h* |
|  | Alkali or alkaline earth metal salt of an Acid with a above 2 at 70–90°C in toluene in the presence of a phase transfer catalyst. |  | *i* |

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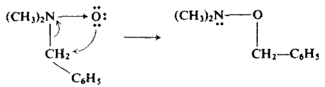
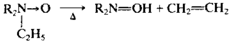
[a] N. V. Khromov-Borisov and T. N. Kononova, Probl. Poluch. Poluprod Prom. Org. Sin., Akad. Nauk S. S. S. R. Otd. Obshch. Tekh. Khim. 9–10 (1967); *Chem. Abstr.* **68,** 48946u (1986). [b] M. Koporska, J. Ostromska, and M. Cieslak, Przem. Chem., *49* (10) 594 (1970); *Chem. Abstr.* **74,** 41800g (1971). [c] K. Jockers, H. Meier, K. H. Koenig, and K. Kartte, Ger. Offen. 2,000,502 (July 15, 1971); *Chem. Abstr.* **75,** 88090m (1971). [d] J. L. Ludec, U.S. Pat. 3,927,101 (Dec. 16, 1975). [e] M. Fleischmann, J. Ghoroghchian, and R. E. W. Janeson, *J. Appl. Electrochem.* **11** *(1) 55 (1981)*; *Chem. Abstr.*, **94,** 74582j (1981). [f] T. M. Grishina, O. K. Lebedeva, and G. D. Vovchenko, Zh. Fiz. Khim. **56** (2) 490 (1982). [g] H. A. Sharma and P. Hope. Eur. Pat. Applic. EP 147,879 (July 10, 1985); *Chem. Abstr.* **103,** 214967q (1985). [h] M. S. Mourad, R. S. Varma, and G. W. Kabalka, *J. Org. Chem.* **50,** 133 (1985). [i] Ciba-Geigy AG, German Pat. DE 3631 172A (3/20/87); Derment Week 8713, Section E, General Chemistry, page DE(A)-E, Abstract E14, 87-087735/13.


(55)

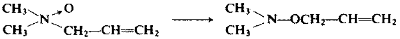
This suggested mechanism does not explain all the details of the reaction since, as seen in Preparation 6-1, water also forms during the decomposition.

The thermal degradation of tertiary amine oxides to give *N*,*N*-dialkylhydroxylamines is a well-known process [52c–52g] and has been reviewed [52h].


$$R_2\underset{C_2H_5}{\underset{|}{N}}\rightarrow O \xrightarrow[\Delta]{} R_2N{=}OH + CH_2{=}CH_2 \qquad (56)$$

The preparation of dimethylhydroxylamines (see Preparation 6-2) has also been reported in a patent [52h] to involve a similar process, wherein the R group is methyl and the other group is an alkyl group of $C_8$ to $C_{18}$, rather than ethyl, as shown in Eq. 56.

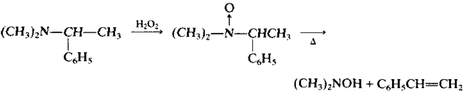
### *6-1. Preparation of* N,N*-Dimethyl-O-allylhydroxylamine* [52]


(57)

Twenty grams (0.24 mole) of allyldimethylamine are oxidized with 10% aqueous hydrogen peroxide. The excess hydrogen peroxide is decomposed by adding platinum foil in the reaction mixture. The mixture is concentrated to a thick syrup under reduced pressure at 60–65°C. The amine oxide is then dehydrated by adding the following reagents in turn and distilling them off under reduced pressure (at a convenient point the platinum is removed): two 50-ml portions of absolute ethanol, three 50-ml portions of benzene, and one 50-ml portion of absolute ethanol.

The residual syrup is heated under a nitrogen atmosphere, under reflux, for 30 min in an oil bath maintained between 105 and 110°C. During this stage, the mixture becomes dark and forms two layers. The condenser is then set down for distillation, and the temperature is raised over a 4-hr period to 140°C. The distillate (product and water) is separated, the aqueous layer is extracted with a 10-ml portion of ether which is combined with the organic layer. The product solution is dried over potassium hydroxide and is then distilled through an adiabatic, total reflux–partial takeoff distillation column with a 1.5 × 15 cm glass-helix-packed section, to afford 12.2 gm (51%), b.p. 83°C, $n_D^{25}$ 1.3982, $d_4^{25}$ 0.7939. The melting point of picrate is 92.5–93.5°C.

### 6-2. *Preparation of* N,N-*Dimethylhydroxylamine Hydrochloride* [52i]



$$(CH_3)_2N{-}\underset{C_6H_5}{CH}{-}CH_3 \xrightarrow{H_2O_2} (CH_3)_2{-}\overset{O\uparrow}{N}{-}\underset{C_6H_5}{CHCH_3} \xrightarrow[\Delta]{} (CH_3)_2NOH + C_6H_5CH{=}CH_2 \qquad (58)$$

(*a*) *Preparation of* N,N-*Dimethyl-(α-phenylethyl)amine Oxide.* To a flask containing 11.0 g (0.074 mole) of *N,N*-dimethyl(α-phenylethyl)amine is added dropwise 18.3 g (0.19 mole) of 35% aqueous hydrogen peroxide, and the mixture is stirred for 11 hr at room temperature. The excess hydrogen peroxide is decomposed by stirring the mixture with 8 sqcm$^2$ clean platinum foil until the evolution of oxygen ceases. Most of the water is removed by distillation at 35 mm Hg, at a bath temperature of 45–55°C. The material that condenses in the dry-ice trichloroethylene trap is saved for recovery in Procedure (b). The residual syrup is diluted with 25 ml of absolute ethanol, and the process is repeated twice while a capillary nitrogen ebulliator is used. The resulting amine oxide is a viscous syrup and has a slight odor of styrene.

(*b*) *Decomposition of* N,N-*Dimethyl-(α-phenylethyl)amine Oxide to* N,N-*Dimethylhydroxylamine.* A 100 ml round bottom flask equipped with a capillary nitrogen inlet, and containing the preceding amine oxide is connected by a large-diameter tube to a condenser set for distillation with two receivers. Each receiver is cooled in a mixture of dry ice and trichloroethylene. The system is evacuated to 5 mm, and the flask is immersed in an oil bath at 85°C. The bath temperature is raised slowly to 115°C over a 35-min period, in which time most of the material distilled over. The bath temperature is finally raised to 150°C, in order to complete the (decomposition) distillation process. The residue remaining averages 0.35 g. The distillate in the dry-ice trap here and from Procedure (a) are combined, pentane is added as a solvent, and the mixture is washed with dilute hydrochloric acid. The acid solution is extracted with pentane, the latter washed with water until neutral.

The product is obtained from the combined aqueous layers containing hydrochloric acid by concentration under reduced pressure, to give a crystalline residue. The latter, upon drying in a vacuum desiccator over $P_2O_5$

averages 6.73 g (94% yield), m.p. 101–101°C (sealed capillary). Recrystallization several times from a mixture of absolute ethanol and ether gives white, hygroscopic needles, m.p. 106.5–109°C (sealed capillary).

| | |
|---|---|
| Analysis Calculated for $C_2H_8NOCl$: | C, 24.62; H, 8.27; N, 14.36; Cl, 36.35. |
| Found: | C, 24.96; H, 8.24; N, 14.12; Cl, 35.99. |

## 7. MISCELLANEOUS METHODS

(1) Hydroxylaminoethylation of aromatic hydrocarbons [149].

(2) Alkylation of hydroxylamine with a methyl sulfide [150].

(3) Substituted hydroxylamines found among the reaction products of nitroxides [151, 152].

(4) Reaction of fluorinated nitroxides with methanol or benzene [153].

(5) Reaction of di-*t*-butylnitroxide with phenylhydrazine in pure methanol under argon to produce *N,N*-di-*t*-butylhydroxylamine [154].

(6) Reaction of an oxime with an aldehyde [9a].

(7) Acylation and rearrangement of formaldehyde phenylhydrazone [155]. [This reaction could not be duplicated (see Renner [20])].

(8) Hydrolysis of 2-alkyl-3-phenyloxaziranes [120]. By the same method *N*-*t*-octylhydroxylamine was prepared (b.p. 50–53°C/0.02 mm Hg, m.p. 40–42°C).

(9) *N*-Methylation of a substituted hydroxylamine with diazomethane [138].

(10) Reaction of trimethylsilane and trifluoronitrosomethane under hydrogenation conditions [28].

(11) Hydrogenation of oximes and *O*-alkyl ethers of oximes [155–157].

(12) Hydrogenation of nitro compounds [158–168].

(13) Electrolytic reduction of oximes and nitro compounds [169–178].

(14) Reduction of 2,3-dimethyl-4-(*O*-nitrophenylthio)-1-phenyl-3-pyrazolin-5-one with sodium borohydride in the presence of palladium on charcoal followed by acidification with acetic acid [179].

(15) Treatment of 6-chloro-2-fluoropurine with hydroxylamine [180].

(16) Preparation and rearrangement of tris(organosilyl)hydroxylamines [181a,b].

(17) Preparation of 1-hydroxy-α-azetidinones [182].

(18) *N,N*-Dimethylhydroxylamine via pyrolysis of amine oxide [183].

(19) Preparation of *N*-alkylhydroxylamines [184].

(20) Dialkylhydroxylamines via oximation of some Mannich bases [185].

(21) Chiral hydroxylamines [186].

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# CHAPTER 11/**OXIMES**

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## 1. INTRODUCTION

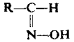
The oximes of ketones and aldehydes have been known for nearly a century. They not only represent a convenient series of derivatives of carbonyl compounds but also may be used as intermediates for the preparation of amides by the Beckmann rearrangement. As will be shown in this chapter, oximes (formerly called "isonitroso compounds") may be prepared by nitrosation of active methylene compounds. By use of this approach, cyclohexane is converted to cyclohexanone oxime, which, after Beckmann rearrangement, produces caprolactam on an industrial scale. Caprolactam is used to manufacture polyamide fibers.

Because oximes may be converted back to aldehydes or ketones, a means of converting active methylene groups to carbonyl compounds by nitrosation may be devised.

Oximes and their derivatives are also of interest as intermediates in pharmaceuticals and pesticides. The new oximinosilanes are finding application in coatings, adhesives, sealants, and polymer additives. Hetero cyclic compounds such as oxazoles, isoxazoles, isoxazolines, triazoles, furazanes, pyrrolines, oxadiazoles, pyrroles, pyridines, isoxazolidinones, carbazoles, and quinoxalines have been produced from oximes.

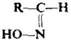
The stereochemistry of oximes has received much attention. Among reviews are standard monographs such as [1–5a] and [5b].

A recent publication on the MM2 force-field parameters for oximes is [5c]. In regard to the geometric isomerism of oximes, the two possible isomers of aldoximes form almost invariably and are readily isolated by fractional crystallization. The structures of these isomers may be written thus:



$$\begin{array}{l} \mathrm{R{-}C{-}H} \\ \quad\ \| \\ \quad\ \mathrm{N{-}OH} \end{array}$$

and



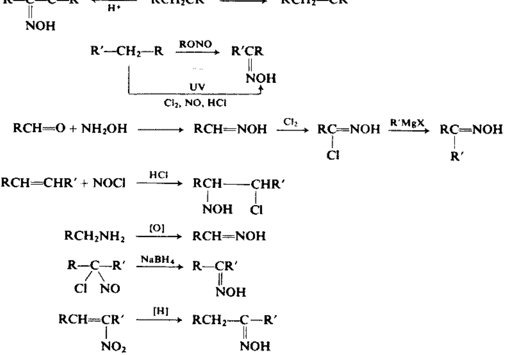
$$\begin{array}{r} \mathrm{R{-}C{-}H} \\ \| \quad\ \\ \mathrm{HO{-}N} \quad\ \end{array}$$

The results of the Beckmann rearrangement of these isomers were considered to be diagnostic in determining the structures involved. For over thirty years, the tacit assumption was that this rearrangement involved the interchange of the hydroxyl group with the group attached to the carbon atom on the same side of the double bond [6]. This observation was considered confirmed by the fact that nitriles formed on dehydration of those isomers which were presumed to have the aldehydic hydrogen and the hydroxyl group on the same side of the double bond, whereas the other isomer did not dehydrate. Only after World War I was new data presented which disputed these assumptions and presented evidence for the generally accepted "trans" mechanism of the Beckmann rearrangement as well as that of the dehydration of oximes [7]. Other work on the configuration of oximes is due to T. W. J. Taylor, of which [8a] is representative.

In the meanwhile, a huge number of oximes had been prepared with their configuration incorrectly given. In fact, a statement has been made that one should consider virtually all structural assignments of oximes made prior to 1925 as the exact reverse of the modern belief in this matter [2]. Unfortunately the situation is not always quite that clear-cut and we can only recommend that all oxime configurations be evaluated carefully. In preparing this chapter an effort was made to ascertain the evidence for the structural assignment before it was accepted by us. Even so we must caution that errors may exist.

The most common methods of preparing oximes are shown in Scheme 1. The two best-known methods are the oximation of carbonyl compounds and the nitrosation of active methylene compounds. Isomerization reactions will also be described in Section 6 of this chapter.

SCHEME 1
Preparation of Oximes

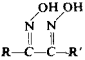


## A. Nomenclature

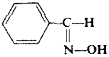
The naming of oximes is relatively simple. Derivatives of aldehydes may be called "aldehyde oxime," "alkanal oxime," or "aldoxime." For example, heptaldehyde oxime, heptanal oxime, or heptaldoxime are all equivalent. Similarly, methyl ethyl ketone oxime, methyl ethyl ketoxime, 2-butanone oxime, and 2-butoxime are all equivalent as far as this ketoxime is concerned.

When higher functions are present in the mixture, the oxime function is indicated as a "hydroxyimino" substituent [8b].

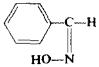
When it comes to configurational assignments, the matter becomes more complex, even if we assume that the true structures are known. Three prefixes are in common use: *syn*, which corresponds to *cis* in the ethylene series; *anti*, which corresponds to *trans* in the ethylene series; and *amphi*, a term used in the naming of dioximes which implies that the two oximes have configurations in which the N—O—H bonds are parallel to each other. Thus the following structure represents an *amphi* isomer.



In the case of aldoximes, *syn* and *anti* refer to the relation of the hydroxyl group to the aldehydic hydrogen. Thus the *syn* form has the hydrogen and hydroxyl groups on the same side of the double bond, the *anti* form has them on opposite sides of the double bond.

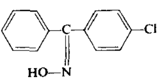


*syn*-benzaldoxime

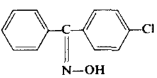


*anti*-benzaldoxime

In the case of unsymmetrical ketoximes it is necessary to state which group is *syn* or *anti* to the hydroxyl [2]. For example,



*syn*-phenyl *p*-chlorophenyl ketoxime
*anti*-*p*-chlorophenyl phenyl ketoxime



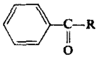
*anti*-phenyl *p*-chlorophenyl ketoxime
*syn*-*p*-chlorophenyl phenyl ketoxime

The nomenclature of the isomers of a dioxime (formerly termed "phenylglyoximes") is indicated below.

The isomers of oximes have also been designated $\alpha$-, $\beta$-, $\gamma$-, or $\delta$-isomers. This nomenclature is found in the older literature, particularly for the dioxime isomers. Usually the $\alpha$-isomer is the one isolated first on oximation of a carbonyl compound because of its insolubility in the reaction medium. In many cases the $\alpha$-form turns out to be the *syn* isomer while the $\beta$-form has the *anti* configuration.

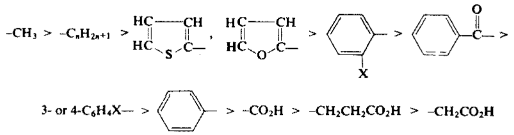
The term "isonitroso" has been used to designate the oximino group in some nomenclature systems. We consider this an unnecessary and unduly confusing method of naming oximes.

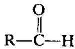
In the preparation of oximes from phenyl ketones of the type



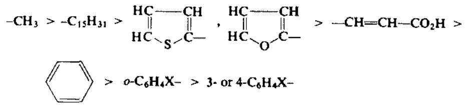
the nature of the R group is said to have an effect on the orientation of the hydroxyl group. Thus, if R is a $CH_3$ group, the ketoxime product will be predominantly of the *syn*-methyl isomer, while if R is a $-CH_2CO_2H$ group, the ketoxime will be predominantly the *anti*-carboxylic acid isomer.

The order of the influence of R groups is as follows [3]:


$-CH_3$ > $-C_nH_{2n+1}$ >
HC—CH
HC S C—
,
HC—CH
HC O C—
>
X
>
O
C— >
3- or 4-$C_6H_4X$— >
> $-CO_2H$ > $-CH_2CH_2CO_2H$ > $-CH_2CO_2H$



In the case of aldehydes of the type $R—\overset{O}{\overset{\|}{C}}—H$, a similar series exists, which by the way, implies that tne *anti* isomers tend to form predominantly. This series is as follows [3]:


$-CH_3$ > $-C_{15}H_{31}$ >
HC—CH
HC S C—
,
HC—CH
HC O C—
> —CH=CH—$CO_2H$ >
> o-$C_6H_4X$– > 3- or 4-$C_6H_4X$–

Recently, the Chemical Abstracts Service and the IUPAC have adopted a new system of naming stereoisomers [9–11]. That aspect of the system that applies to oximes is outlined here.

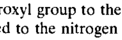
1. The groups attached to doubly bonded atoms have been arranged in order of sequence-rule preference. The method of arriving at this sequence is beyond the scope of this book; however, common groups and their sequence numbers are listed in Table I [11].

To be noted here for our purposes is that hydrogen is lowest in order of importance, followed, roughly, by the lower alkyls in order of increasing chain length, aromatic groups, and ending with the halo groups in order of increasing atomic weight.

2. Since we are dealing with oximes in which one of the doubly bonded atoms is a nitrogen bearing a single hydroxyl group, the concern is only with the relation of the hydroxyl group to the two groups attached to the carbon atom which is bonded to the nitrogen by a double bond.

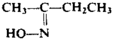
3. The sequence numbers are assigned to the two groups attached to the two groups attached to the doubly bonded carbon.

4. The relation of the hydroxyl group to the group with the *higher sequence number* is determined. If they are on the same side of the plane of double bond, the compound is assigned the descriptor Z (from the German, *zusammen*, together); if they are on opposite sides of the plane, the descriptor E (from the German, *entgegen*, opposite) is used. Thus,



$$\begin{array}{l} CH_3\text{—}\underset{\|}{C}\text{—}CH_2CH_3 \\ \qquad\;\, N\text{—}OH \end{array}$$

is Z-2-butanone oxime (or Z-methyl ethyl ketone oxime, etc.), while



$$\begin{array}{l} CH_3\text{—}\underset{\|}{C}\text{—}CH_2CH_3 \\ HO\text{—}N \end{array}$$

is E-2-butanone oxime (or E-methyl ethyl ketone oxime, etc.).

5. In the case of aldoximes, since hydrogen has the lowest possible preference number, all *syn*-aldoximes become E-aldoximes and all *anti*-aldoximes become Z-aldoximes.

It has been pointed out that the choice of the descriptors E and Z is not entirely felicitous. The letter Z has a "transoid" character while E is "cisoid," thus giving an intuitive picture opposite to the correct one [12a]. Furthermore while *zusammen* does mean "together" and *entgegen* "opposite," the word *entgegen*, unfortunately for the present system, has also a connotation of "togetherness" in such phrases as *entgegen kommen* (to come together, to approach), *entgegen fahren* to drive to meet) (cf. also [12b]).

## TABLE I

### SOME COMMON GROUPS IN ORDER OF SEQUENCE-RULE PREFERENCE[a]

---

A. Alphabetical Order (Higher Number Denotes Greater Preference)

| | |
|---|---|
| 65 | Acetoxy |
| 36 | Acetyl |
| 48 | Acetylamino |
| 21 | Acetylenyl |
| 10 | Allyl |
| 43 | Amino |
| 44 | Ammonio $^+H_3N$– |
| 37 | Benzoyl |
| 49 | Benzoylamino |
| 65 | Benzoyloxy |
| 50 | Benzyloxycarbonylamino |
| 13 | Benzyl |
| 60 | Benzyloxy |
| 41 | Benzyloxycarbonyl |
| 75 | Bromo |
| 42 | *t*-Butoxycarbonyl |
| 5 | *n*-Butyl |
| 16 | *sec*-Butyl |
| 19 | *t*-Butyl |
| 38 | Carboxyl |
| 74 | Chloro |
| 17 | Cyclohexyl |
| 52 | Diethylamino |
| 51 | Dimethylamino |
| 34 | 2,4-Dinitrophenyl |
| 28 | 3,5-Dinitrophenyl |
| 59 | Ethoxy |
| 40 | Ethoxycarbonyl |
| 3 | Ethyl |
| 46 | Ethylamino |
| 68 | Fluoro |
| 35 | Formyl |
| 63 | Formyloxy |
| 62 | Glycosyloxy |
| 7 | *n*-Hexyl |
| 1 | Hydrogen |
| 57 | Hydroxy |
| 76 | Iodo |
| 9 | Isobutyl |
| 8 | Isopentyl |
| 20 | Isopropenyl |
| 14 | Isopropyl |
| 69 | Mercapto |
| 58 | Methoxy |
| 39 | Methoxycarbonyl |
| 2 | Methyl |
| 45 | Methylamino |
| 71 | Methylsulfinyl |
| 66 | Methylsulfinyloxy |
| 72 | Methylsulfonyl |
| 67 | Methylsulfonyloxy |
| 70 | Methylthio |
| 11 | Neopentyl |
| 56 | Nitro |
| 27 | *m*-Nitrophenyl |
| 33 | *o*-Nitrophenyl |
| 24 | *p*-Nitrophenyl |
| 55 | Nitroso |
| 6 | *n*-Pentyl |
| 61 | Phenoxy |
| 22 | Phenyl |
| 47 | Phenylamino |
| 54 | Phenylazo |
| 18 | Propenyl |
| 4 | *n*-Propyl |
| 29 | 1-Propynyl |
| 12 | 2-Propynyl |
| 73 | Sulfo |
| 25 | *m*-Tolyl |
| 30 | *o*-Tolyl |
| 23 | *p*-Tolyl |
| 53 | Trimethylammonio |
| 32 | Trityl |
| 15 | Vinyl |
| 31 | 2,6-Xylyl |
| 26 | 3,5-Xylyl |

### B. Increasing Order of Sequence-Rule Preference

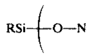
1 Hydrogen
2 Methyl
3 Ethyl
4 *n*-Propyl
5 *n*-Butyl
6 *n*-Pentyl
7 *n*-Hexyl
8 Isopentyl
9 Isobutyl
10 Allyl
11 Neopentyl
12 *2-Propynyl*
13 Benzyl
14 Isopropyl
15 Vinyl
16 *sec*-Butyl
17 Cyclohexyl
18 1-Propenyl
19 *t*-Butyl
20 Isopropenyl
21 Acetylenyl
22 Phenyl
23 *p*-Tolyl
24 *p*-Nitrophenyl
25 *m*-Tolyl
26 3,5-Xylyl
27 *m*-Nitrophenyl
28 3,5-Dinitrophenyl
29 1-Propynyl
30 *o*-Tolyl
31 *2,6-Xylyl*
32 Trityl
33 *o*-Nitrophenyl
34 2,4-Dinitrophenyl
35 Formyl
36 Acetyl
37 Benzoyl
38 Carboxyl
39 Methoxycarbonyl[b]
40 Ethoxycarbonyl[b]
41 Benzyloxycarbonyl[b]
42 *t*-Butoxycarbonyl[b]
43 Amino
44 Ammonio $^{+}H_3N-$
45 Methylamino
46 Ethylamino
47 Phenylamino
48 Acetylamino
49 Benzoylamino
50 Benzyloxycarbonylamino
51 Dimethylamino
52 Diethylamino
53 Trimethylammonio
54 Phenylazo
55 Nitroso
56 Nitro
57 Hydroxy
58 Methoxy
59 Ethoxy
60 Benzyloxy
61 Phenoxy
62 Glycosyloxy
63 Formyloxy
65 Acetoxy
65 Benzoyloxy
66 Methylsulfinyloxy
67 Methylsulfonyloxy
68 Fluoro
69 Mercapto HS–
70 Methylthio $CH_3S-$
71 Methylsulfinyl
72 Methylsulfonyl
73 Sulfo $HO_3S-$
74 Chloro
75 Bromo
76 Iodo

---

[a] ANY *alteration to structure, or substitution, etc. may* alter the order of preference. [b] These groups are ROC(=O)–. [Reprinted from *J. Org. Chem.* **35**, 2849 (1970). Copyright 1970 by the American Chemical Society. Reprinted by permission of the copyright owner.]

### B. Safety Notes

In 1974, L. J. Tyler reported two potentially devastating explosions during the preparation of ketoximosilanes of structure



$$RSi\left(O{-}N{=}C\begin{matrix}C_2H_5\\CH_3\end{matrix}\right)_3$$

The explosions were attributed to the inadvertent development of acidic conditions in the system, which may have led to highly exothermic Beckmann rearrangement conditions.

Further experiments showed that whereas methyl ethyl ketoxime can be distilled in the presence of impurities, the compound undergoes violent degradation when heated to 50–70°C. Among the impurities that may cause explosions are acids, the hydrochloride salt of methyl ethyl ketoxime, and ferric chloride. A level of 2% of ferric chloride lowered the onset of violent degradation to 50°C [12c].

A cursory review of the preparations given in this chapter showed that virtually every one, at some stage of the process, has the oxime product in an acidic medium. We therefore believe that, while this potential hazard needs further study, great care in the preparation of handling of oximes must be exercised. Precautions must be taken particularly because oximes are such common derivatives, prepared in the student laboratory for the identification of carbonyl compounds by the melting point of their oximes.

Furthermore, many of the syntheses discussed in this chapter involve the use of hydroxylamine or its salts. A report based on a Safety Newsletter of the National Safety Council states that hydroxylamine, its salts, and mother liquors containing these materials have been known to explode on warming [13]. The causes and conditions for explosion are not well understood. Therefore, due precautions must be exercised in handling hydroxylamine, its salts, and solutions containing these compounds.

## 2. CONDENSATION REACTIONS

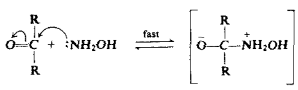
### A. Oximation of Aldehydes and Ketones

The reaction of hydroxylamine with a carbonyl compound is a widely used and well-known method of preparing derivatives of aldehydes and ketones (14–55a–55m). As expected, aldehydes usually react more rapidly than ketones and aliphatic aldehydes are more reactive than aromatic aldehydes. Some highly hindered ketones are inert unless drastic reaction conditions are used.

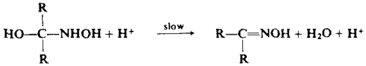
In a study of the kinetics of oximation of a large number of ketones, it was generally found that methyl ketones react more rapidly than ethyl ketones and these, in turn, react more rapidly than propyl ketones, and so on [14].

That the rate of oximation is profoundly influenced by the pH of the reaction medium was recognized early and studied extensively [15a–e]. Briefly summarized, the observations are that in the reaction of hydroxylamine with acetone, as the pH rises from 2 to approximately 5, the rate of oxime formation increases dramatically. Between pH 5 and 7, the rate drops again. In effect the rate vs. pH curve is bell shaped. On the alkaline side, beyond pH 8, the rate of oximation again becomes rapid. The mechanism of the base-catalyzed oximation is quite complex.

On the acidic side of the pH scale, the reaction mechanism has been visualized as a two-step process which initially involves the rapid nucleophilic addition of hydroxylamine to the carbonyl function, followed by a slow, specific, and general acid-catalyzed dehydration.



$$R_2C{=}O + {:}NH_2OH \xrightleftharpoons{\text{fast}} \left[ {}^{-}O{-}CR_2{-}\overset{+}{N}H_2OH \right] \xrightleftharpoons{\text{fast}} HO{-}CR_2{-}NHOH \qquad (1)$$



$$HO{-}CR_2{-}NHOH + H^+ \xrightarrow{\text{slow}} R{-}\underset{R}{C}{=}NOH + H_2O + H^+ \qquad (2)$$

At low pH, the level of free hydroxylamine is reduced because of protonation so that, in effect, the addition step (Eq. 1) becomes rate-determining at low pH even though the acid-catalyzed dehydration (Eq. 2) is expected to be rate determining. As the pH increases, reaction conditions are found in which the rates of the two reaction steps are balanced properly for rapid oxime formation. This pH level is in the range of 4–5 [16]. For this reason, many oximations are carried out in a reaction medium buffered with sodium acetate–acetic acid.

The mechanism of oximation on the basic side (pH 6–12) has been studied more recently [17]. The reactions involved are evidently more complex than those on the acid side. The nature of the carbonyl compounds seems to effect the reaction mechanism. Both in the case of benzaldehyde and acetone the reaction appears to depend on oxonium ions and hydroxide ions. In the case of acetone, a reaction which is independent of pH was also noted. The reaction appears to be catalyzed by water. The catalysis by oxonium ions and by water are considered cases of general acid catalysis, the reaction involving hydroxide ions is interpreted to be a case of specific hydroxide ion catalysis.

A new study of the equilibrium constant for the formation of pyruvic oxime at various pH's indicates that there is a large equilibrium constant for pyruvic oxime formation and a small rate constant for the rate of hydrolysis at a neutral pH. This implies that at a neutral pH, pyruvic oxime is quite stable to hydrolysis.

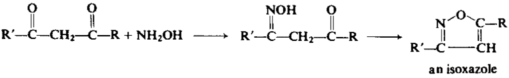
From the preparative standpoint several points should be kept in mind. First of all, oximation is reversible, particularly under acid conditions [18]. Use of this fact may be made to prepare unusual carbonyl compounds. Specifically, as will be discussed later, active methylene compounds, on treatment with nitrous acid, usually form oximes. On hydrolysis, the oximated methylene group will be converted to a carbonyl group. Under acidic conditions, in some cases even in the presence of water, oximes may undergo Beckmann rearrangements to give amides. While this rearrangement is beyond the scope of this chapter, it may constitute a cause for reductions in yields of isolatable oximes.

Oximes, and particularly 1,2-dioximes, exhibit a great tendency to complex with metal ions. Therefore the use of chelating agents might be considered in the preparation of high-purity oximes, if it were not for the observation that metal impurities may render oximes subject to violent degradations at slightly above room temperatures [12c].

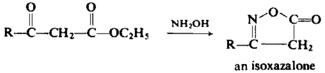
Despite this, in the preparation of 1,2-cyclohexanedione dioxime ("Nioxime"), small amounts of iron impurities are removed from the oximating reagent by (1) adding a small amount of previously prepared dioxime to this solution, (2) decolorizing the resultant red solution with carbon, and (3) filtering. Then the oximating solution is ready for the preparation of the main batch of the oximes [19]. Similar procedures may well be used in the preparation of many oximes, with due precautions.

Another matter which is not always carefully considered in the preparative literature is that oximes are amphoteric and may act either as weak acids or weak bases. Therefore both sodium salts and hydrochloride salts can be formed. The solubility of these salts may vary with the nature of the isomer at hand. Usually the free oximes may be regenerated from the sodium salt form by treatment with carbon dioxide and from the hydrochloride salt by treatment with sodium carbonate.

While compounds with more than one carbonyl function can generally react with more than one equivalent of hydroxylamine, compounds in which two carbonyl groups are $\beta$ to each other form cyclic compounds, that is, isoxazoles in the case of $\beta$-diketones (Eq. 3) and isoxazolones in the case of $\beta$-keto esters (Eq. 4).



(3)



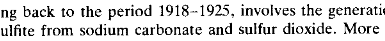
(4)

When oximes are to be prepared for identification purposes, the usual method of preparation simply involves treatment of the carbonyl compound with hydroxylamine in an aqueous medium. If necessary, the pH may be adjusted, and ethanol may be added to enhance mutual solubility of reagents. The reactants may simply be shaken at room temperature or warmed gently on a steam bath. On cooling in ice, oximes frequently will separate out. Since some oximes are liquids or oil-out because of improper levels of solvents or reactants being used, other carbonyl reagents such as 2,4-dinitrophenylhydrazine, phenylhydrazine, or semicarbazide are usually preferable to prepare derivatives.

While the free base, hydroxylamine, may be used directly to prepare oximes, because of storage problems, it is more usual to prepare hydroxylamine as required *in situ* from the hydrochloride or sulfate salts with a variety of alkaline reagents as is shown in Table II.

A reagent which seems to have been forgotten, although several preparations using it are given in *Organic Syntheses*, is sodium hydroxylamine disulfonate [20a,b, 21]. This reagent is readily prepared by reduction of sodium nitrite with sodium bisulfite and sulfur dioxide. The original literature, going back to the period 1918–1925, involves the generation of sodium bisulfite from sodium carbonate and sulfur dioxide. More recently, commercial sodium bisulfite in the presence of sulfur dioxide has been used [21, 22]. A classical method of preparing a standard solution of sodium hydroxylamine disulfonate is given here. Some disagreement exists in the literature as to the exact nature of this reagent. Sometimes it is referred to as sodium hydroxylamine monosulfonate [21, 22].

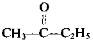
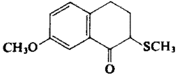
### *2-1. Preparation of Sodium Hydroxylamine Disulfonate* [23]

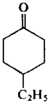
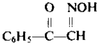
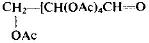
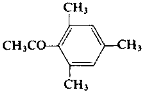


$$NaNO_2 + NaHSO_3 + SO_2 \longrightarrow \left[HO{-}N\begin{matrix}SO_3\\SO_3\end{matrix}\right]^{2-} + 2Na^+ \qquad (5)$$

## TABLE II

### OXIMATION OF ALDEHYDES AND KETONES

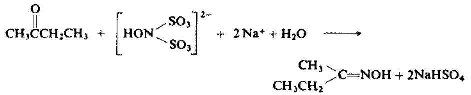
| Aldehyde RCH=O (moles) | Ketone R—CR′ ‖ O (moles) | Hydroxylamine reagent (moles) | Base (moles) | Solvent (ml) | Reaction conditions | | Yield (%) | B.p., °C (mm Hg) or m.p., °C | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Temp. (C°) | Time (hr) | | | |
| — |  $CH_3-\overset{\overset{O}{\|}}{C}-C_2H_5$<br>(1.0) | $HON(SO_3)_2Na_2$<br>(1.2) | — | $H_2O$<br>(930) | 70 | 12 | 75 | 152–154<br>(760) | 24 |
| $CH_3-CH=O$<br>(4.55) | — | $HONH_3 + Cl$<br>4.68 | $Na_2CO_3$<br>(2.55) | $H_2O$<br>(600) | 0–10 | 18–20 | 80 | 112–114<br>(760) | 26 |
| $C_6H_5CH=O$<br>(2.0) | — | 2.06 | NaOH<br>(5.0) | $H_2O$<br>(600)<br>95% | 25–70 | 1 | 88 | 129.5–130<br>(anti) | 29 |
| — | <br>(0.02) | 0.05 | NaOH<br>(0.05)<br>30% | $C_2H_5OH$<br>(100) | 0–10 | 1–2 | 64 | 107.9–108.8 | 31 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| — |  (1.2) | 1.44 | $NH_4OH$ (1.44) | $H_2O$ (1000) | 0–10<br>80–90 | 1–2 | 92 | 120–124 (10) | 35 |
| — |  $C_6H_5—\overset{\overset{\displaystyle O}{\parallel}}{C}—\overset{\overset{\displaystyle NOH}{\parallel}}{CH}$ (0.34) | 0.35 | $NaOCOCH_3$ (0.6) | $C_2H_5OH$ (150) | 100 | 4 | 92 | 150–158 | 36 |
| —<br>— |  $\underset{\underset{\displaystyle OAc}{\vert}}{CH_2}—[CH(OAc)_4CH{=}O$ (0.0254) | 0.0331 | $K_2CO_3$ (0.051) | $H_2O$ (100) | 25 | 1–2 | 71 | 99–99.5 | 37 |
| — | 2-Acetylphenanthrene (0.0091) | 0.0232 | Pyridine (12 ml) | $C_2H_5OH$ (4) | 100 | 3 | 97 | 196–197 | 39 |
| — |  (0.062) | 0.08 | K—O—Amyl (0.2) | *t*-Amyl alc. (100) | 25 | 32 | 86 | 101.5–102.5 | 51 |

In a 5-liter flask equipped with an efficient stirrer and surrounded with a large ice–salt bath is placed 4-liters of distilled water, 325gm (3 moles) of anhydrous sodium carbonate, and 420 gm (5.8 moles) of 95% pure sodium nitrite. The mixture is stirred and cooled. When the temperature has reached −5°C, sulfur dioxide is passed into the solution at such a rate that the solution temperature never exceeds 0°C. With efficient cooling, the reduction is completed in approximately 4 hr. The end of the reduction is indicated by a drop in the pH of the solution to the acid side. Just before the reaction turns acid, the solution becomes slightly brown in color. The solution is approximately 1.2 *M* in sodium hydroxylamine disulfonate and may be used directly for the preparation of oximes.

In using sodium hydroxylamine disulfonate, the reagent is treated with a carbonyl compound, warmed, and cooled. Only at this point is the reaction mixture neutralized with an alkaline solution [24]. This method is suitable for the preparation of a range of carbonyl compounds. Negative results were obtained in the case of benzil and quinone monoxime, either because the oximes are not sufficiently soluble in the reaction medium or because the oximes produced are not stable in the acidic reaction solution.

## *2.2. Preparation of Methyl Ethyl Ketoxime* [24]

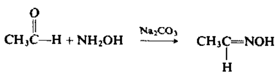


$$CH_3\overset{O}{\overset{\|}{C}}CH_2CH_3 + \left[HON\begin{matrix}SO_3\\SO_3\end{matrix}\right]^{2-} + 2Na^+ + H_2O \longrightarrow \begin{matrix}CH_3\\CH_3CH_2\end{matrix}\!>C{=}NOH + 2NaHSO_4 \qquad (6)$$

With suitable precautions, to 1 liter of the sodium hydroxylamine disulfonate solution from Preparation 2-1 (approx. 1.2 moles) is added 72 gm (1 mole) of methyl ethyl ketone. The mixture is warmed to 70°C. Then the reaction flask is wrapped with insulation and allowed to cool slowly for 12 hr.

After neutralization with 48% sodium hydroxide solution, the oxime is extracted from the reaction mixture with benzene. The benzene solution is distilled fractionally. The product distills between 152° and 154°C; yield, 65 gm (75%).

## *2-3. Preparation of Acetaldoxime* [26]



$$CH_3\overset{O}{\overset{\|}{C}}{-}H + NH_2OH \xrightarrow{Na_2CO_3} CH_3\underset{H}{\underset{|}{C}}{=}NOH \qquad (7)$$

With suitable precautions, to a solution of 325 gm (4.68 moles) of hydroxylamine hydrochloride in 300 ml of water mixed with a solution of 255 gm (2.55 moles) of sodium carbonate in 600 ml of water, cooled in an ice–salt mixture, is added dropwise, with stirring, a solution of 200 gm (4.55 moles) of acetaldehyde in 100 ml of water. After standing overnight, the solution is saturated with sodium chloride and the product is separated by repeated extractions with ether.

The combined ether extracts are dried over calcium chloride, filtered, and distilled to afford 215 gm (80%), b.p. 112–114°C (760 mm Hg).

Because many aldehydes are not very water soluble, this reaction may be carried out either with vigorous stirring or by adding sufficient alcohol to make the reaction mixture homogeneous [27]. When the product has to be purified by distillation, it has been recommended that the flask be immersed into an oil bath maintained at a constant temperature above the anticipated boiling point of the product rather than warming the product and oil bath up to the boiling range from room temperature. By this technique heptaldoxime, b.p. 103–107°C (66 mm Hg), m.p. 53–55°C, cyclohexanone oxime, b.p. 100–105°C (10–12 mm Hg), m.p. 87–88°C [27]; and methyl ethyl ketoxime, b.p. 150–155°C [28], have been prepared.

The treatment of a carbonyl compound with a hydroxylamine salt, with or without a solvent (or water), and with a neutralization step of the hydroxylamine salt using a simple base may be considered as a general preparative procedure. Examples of the method have been cited in this chapter. Some recent examples are the preparation of 6-methyl-hept-5-en-2-one oxime (b.p. 110–115°C) at 8 mm; 'H NMR δ 1.60 (3H, *br s*), 1.67 (3H, *br s*), 2.27 (3H, *t*, J = 1.8 Hz), 2.0–2.5 (4H, *m*), 4.90–5.3 (1H, *br m*), 9.3-9.6 (1H *br s*); IR 3250, 1665, 1360, 1340 cm$^{-1}$] [55b]; the oxime of 5,7-diphenyl-1,3-diazaadamantan-6-one (55f) and of acetylenic aldehydes of the structure

$$R-(C{\equiv}C)_n-CHO$$

where $R = CH_3O_2CCH=CH$, $n = 1$ to 3; $R = C_6H_5$, $n = 1$ or 2; $R = HO\,(CH_2)_2$, $n = 2$ or 3 [55g].

Corey and co-workers recommend that an oxime be prepared by treating 1 mole of a ketone (2,3-epoxycyclohexanone, in this case) with 1.1 moles of hydroxylamine hydrochloride and 2.2 moles of sodium acetate in methanol (10 ml of methanol/g of hydroxylamine hydrochloride) at 0°C for 30 min. The product is worked up by solvent extraction and recrystallization from petroleum-ether–ether. The yield of 2,3-epoxycyclohexanone oxime by this method is 95%, m.p. 84–85°C [55m]. By a similar procedure, pentacyclo [$5.3.0.0^{2,6}.0^{3,10}.0^{4,8}$] decane-5,9-dione dioxime was prepared in an 86% yield [55c]. We are designating this process Method A.

By this procedure, (Method A), the yield of (Z)-*trans*-4-*tert*-butyl-2-chlorocyclohexan-1-one oxime was only 63%, of which more than 95% was Z-isomer, m.p. 82–83.5°C [55h].

(Z)-cis-2-chloro-3-methylcyclohexan-1-one oxime was formed in 71% yield, 82% Z-isomer.

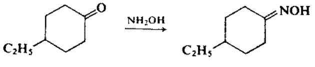
A variation of the Corey method (Method B), involving 0.5 moles of glacial acetic acid, 1.5 molar equivalents of potassium acetate, and 1.5 molar equivalents of hydroxylamine hydrochloride per mole of alpha-chloroketone reacted at room temperature for 0.5–1.5 hr, afforded the E-isomer of the same ketone in 89% yield, 90% E-isomer, m.p. 88–93°C. [55h]. By this method (E)-*cis*-4-*tert*-butyl-2-chlorocyclohexan-1-one oxime was formed in 82% yield, more than 95% E-isomer, m.p. 135–136°C (dec.); (E)-*cis*-2-chloro-3-methylcyclohexan-1-one oxime was formed in 82% yield, 80% E-isomer, b.p. 100°C (0.5 mm Hg), and (E)-*trans-z*-chloro-3-methylcyclohexan-1-one oxime was formed in 53% yield, more than 95% E isomer, m.p. 109.5–110.5°C [55h].

*Method C.* A third method involves stirring a solution of an alpha-chloroketone in dry chloroform (approx. 0.33 mole). To this solution is added 2.0 molar equivalents of *O*-(*tert*-butylmethylsilyl)hydroxylamine along with activated 4-Å molecular sieve under argon for 18–72 hr. The product from the work-up was purified by $SiO_2$-gel chromatography and/or distillation.

By Method C were prepared the following: (E)-*cis*-4-*tert*-butyl-2-chlorocyclohexan-1-one (*tert*-butyldimethylsilyl) oxime in 92% yield, more than 95% E isomer, b.p. 110°C (at 0.07 mm Hg); and (E)- and (Z)-*cis*-2-chloro-3-methyl cyclohexan-1-one (*tert*-butyldimethylsilyl) oxime in 91% yield, ratio E to Z isomers 1:1, b.p. 80°C (at 0.07 mm Hg). Other silylated oximes are also mentioned in [55h].

To be noted in this brief discussion is that Method B quite surprisingly is selective in forming the E-oxime, whereas Method A produces the Z-oxime, provided the chlorine is axial [55h].

### *2-4. Preparation of 1-Ethyl-4-cyclohexanone Oxime* [35]



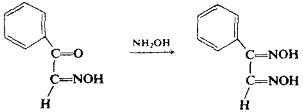
(8)

To a solution of 100 gm (1.44 moles) of hydroxylamine hydrochloride in 1-liter of water is added dropwise 150 gm (1.2 moles) of 1-ethyl-4-cyclohexanone. As a scavenger of the liberated hydrochloric acid, the reaction mixture is neutralized with 30% aqueous ammonia. Finally the solution is warmed briefly at 80–90°C. On cooling the oxime separates as a reddish brown, viscous layer on the aqueous phase. The product layer is separated and the aqueous layer is repeatedly extracted with methylene dichloride or benzene. The combined product layer and extract is dried with sodium sulfate, filtered, and freed of solvent by evaporation.

The crude product is purified by distillation, b.p. 120–124°C (10 mm Hg), $d_4^{20}$ 0.982, $n_D^{20}$ 1.4889. The viscous fluid forms a glass at −25°C. The yield is 154 gm (92%).

By similar procedure the following were prepared: 1,3-dimethyl-5-cyclohexanone oxime, b.p. 118–120°C (13 mm Hg), m.p. 72–73°C; 1-isopropyl-4-cyclohexanone oxime, b.p. 124°C (7 mm Hg); 1-isopropyl-2-cyclohexanone oxime, b.p. 129°C (4 mm Hg); 1-*t*-butyl-4-cyclohexanone oxime, m.p. 133°C; 1-hexahydrobenzyl-4-cyclohexanone oxime, b.p. 133°C (2 mm Hg), m.p. 127°C.

### *2-5. Preparation of Phenylglyoxime* [36]

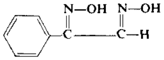


(9)

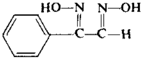
To a solution of 50 gm (0.34 mole) of ω-oximinoacetophenone (ω-isonitrosoacetophenone) in 150 ml of ethanol is added to a solution of 48 gm (0.595 mole) of sodium acetate and 24 gm (0.345 mole) of hydroxylamine hydrochloride in 75 ml of water. The mixture is heated at reflux for 4 hr.

After cooling, a large portion of the solvent is evaporated off under reduced pressure. The mixed crude product, which precipitates, is filtered off, washed with water, and air-dried to afford 51 gm (92%), m.p. 150–158°C.

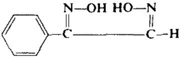
The separation of the three isomers by fractional crystallization procedures depends on the relative ratio of the components in the mixture, the concentration of the components in the solvent, the length of time the solvent–product mixture is heated, etc. It is therefore important that the progress of the crystallization be followed by thin-layer chromatography using freshly prepared tlc plates [Merck (Darmstadt) silica gel G is recommended as the coating]. The suggested tlc solvent is benzene–ethyl acetate (7:3), detection by iodine vapor; 0.45 $R_f$ for *anti*-phenyl-*amphi*-glyoxime (I), 0.40 $R_f$ for phenyl-*anti*-glyoxime (II), and 0.35 $R_f$ for phenyl-*syn*-glyoxime (III).



(I)



(II)



(III)

*Anti*-phenyl-*amphi*-glyoxime (I) is separated from the mixed product by repeated recrystallization from acetone–chloroform (or alcohol–water), m.p. 178–180°C; UV, $\lambda_{max}$ (95% ethanol) 230 m$\mu$ ($\epsilon$ 14,800).

Phenyl-*anti*-glyoxime (II) is isolated from the mother liquor of the first crystallization in the separation of (I). The residue from the evaporation of this mother liquor is crystallized repeatedly from acetone–chloroform. After sublimation, the properties of the material are as follows: sublimation temperature, 90°C (0.2 mm Hg); m.p. 166–168°C; UV, $\lambda_{max}$ (95% ethanol) 228 m$\mu$ ($\epsilon$ 14,380). Only about 1% of pure isomer is isolated from the starting product.

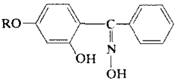
Phenyl-*syn*-glyoxime (III) is isolated by crystallizing the starting product from a dilute solution of ethyl acetate, m.p. 168–170°C; UV, $\lambda_{max}$ (95% ethanol) 252 m$\mu$ ($\epsilon$ 12,200).

The preparation of oximes derived from highly hindered ketones has been a problem for many years. By use of high pressures (140,000 psi), some 11-keto steroids, hexamethylacetone, and pentamethylacetone have been oximated with hydroxylamine in an acetate buffer. The reported melting points of the oximes are hexamethylacetone oxime, m.p. 157.5–158.5°C; pentamethylacetone oxime, m.p. 140–141°C [50].

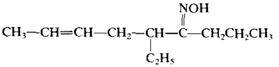
An approach which is more in the realm of the ordinary synthetic laboratory involves prolonged reaction times in the presence of a strong basic catalyst, potassium tertiary amylate in tertiary amyl alcohol. Yields were found to be substantially better when prolonged reaction times at room temperature (1–6 months) were used instead of heating. For this reason, these procedures have been termed "lethargic reactions".

The method seems to have wide applicability, but failed in the case of anthraquinone and 2,3,5,6-tetrachloroacetophenone. In the latter case, 1,2,4,5-tetrachlorobenzene was identified among the reaction products. [51].

In most of the previously mentioned procedures, the hydroxylamine salts were neutralized with relatively mild bases (ammonia, sodium acetate, potassium acetate, sodium carbonate, etc.). However, sodium hydroxide has also been used [31,55d,e]. In the latter two patents, oximes of the structure



where R = alkyl such as octyl [55d] and compounds of structures such as



$$CH_3{-}CH{=}CH{-}CH_2{-}\underset{\displaystyle C_2H_5}{\underset{|}{CH}}{-}\overset{\displaystyle NOH}{\overset{\|}{C}}{-}CH_2CH_2CH_3$$

which is of the general formula $RR'C=NOH$, where R = $\gamma$, $\delta$-alkenyl, R′ = alkyl groups of 1 to 4 carbon chains such that $R + R' = C_{10}$ to $C_{13}$ are discussed [55e].

Oximations have also been carried out in pyridine as a reaction solvent and as the base to form free hydroxylamine for the reaction. This reaction must be carried out with caution because the crude product is usually treated with acids to remove excess pyridine. This may set up the aforementioned hazardous conditions. One compound prepared in pyridine is *N*′-carbomethoxy-*N*-(10,11-dihydro-11-(hydroxyimino)-5,10-methano-5H-dibenzo [a,d] cycloheptan-12-yl)methylamine [55j].

Whereas oximes are most commonly prepared from aldehydes and ketones, acetals may be simultaneously hydrolyzed and oximated under acidic conditions. For example, 1-methyl-2-(dimethoxymethyl)-quinolinium iodide was converted to the corresponding aldoxime by treatment of the starting material, with hydroxylamine hydrochloride in 6% aqueous hydrochloric acid at 100°C for 90 min [55i].

In some cases, the separation of an oxime or an oxime ether from contaminating starting carbonyl compounds is troublesome. Haley and Yates [55k] applied the chemistry of Girard's T reagent to solve this problem. Girard's reagent, $[(CH_3)_3{}^+NCH_2CONHNH_2]\ Cl^-$, reacts with the unreacted carbonyl compounds to form a water-soluble derivative. The water-soluble product is separated from the desired oxime or oxime ether by extracting the oxime with methylene chloride and then concentrating the methylene chloride solution to give the oxime free of the carbonyl compound.

## B. Alkylation of Oxime Dianions

In many cases carbon atoms that bear protons and that are located alpha to a carbonyl group may be considered active methylene compounds.

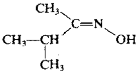
Conversion of the carbonyl to an oxime group still retains some of the active methylene properties of the alpha carbon atom.

The alkylation of aromatic ketoximes in the presence of two equivalents of a strong base had already been reported by Hauser and co-workers [55n]. More recent work addressed the stereochemistry of the reaction [55b,o].

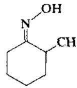
The treatment of acetone oxime with two equivalents of *n*-butyllithium in THF at 0°C led to formation of the *syn*-dianion, which was alkylated with methyl iodide to *syn*-ethyl methyl ketoxime in 73% yield (direct oximation of MEK afforded a *syn*-*anti*-mixture consisting of only 26% of the *syn* isomer [55r].

Upon repeating this reaction, alkylation of *syn*-ethyl methyl ketoxime with 2 equiv. of *n*-butyllithium, followed by methyl iodide, led to alkylation of the alpha-carbon atom with the formation of a 81% yield of *syn*-isopropyl methyl ketoxime, free of the *anti*-isomer (see Preparation 2-6).

When a similar reaction was run with a compound in which the *syn*-carbon was disubstituted, as for example in the following structures,

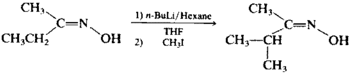


or



metalation with *s*-butyllithium was extremely slow, and, upon addition of methyl iodide, only approx. 25% yields of the *anti*-methylated products were observed. A discussion of the possible causes of these observations can be found in [55o].

### *2-6. Preparation of* syn-*Isopropyl Methyl Ketoxime* [55o]



(10)

To a dry flask fitted with magnetic stirrer (which is closed with a septum) and containing a solution of 0.96 g (11 mmol) of *syn*-ethyl methyl ketoxime (prepared by a similar technique as described herein, using acetone oxime, 2 equiv. of *n*-butyllithium and methyl iodide) in 40 ml of dry tetrahydrofuran at −78°C is added a solution of 8.9 ml of 2.4 molar (22 mmol) of *n*-butyllithium in hexane over a 10-min period. The temperature of the mixture is raised in an ice bath for 20 min and again cooled in dry-ice–

acetone to −78°C. Then, with a syringe, 0.96 ml (11 mmol) of methyl iodide is added. The mixture is warmed to 25°C and stirred for 45 min. After cautious addition of the reaction mixture to water, *syn*-isopropyl methyl ketoxime was isolated from the mixture. Yield 0.91 g (81%).

By similar techniques, the following oximes were prepared [55b].

6-Chlorohept-5-en-2-one oxime (89% yield; b.p. 110°C at 0.6 mm Hg; IR 3610, 3280, 1670, 1370 $cm^{-1}$)

6-Chlorohex-5-en-2-one oxime (85–94% yield; b.p. 79°C at 0.43 mm Hg; IR 3250, 3020, 1665, 1632, 1445, 1370 $cm^{-1}$)

6-Phenylhex-5-en-2-one oxime (65% yield, b.p. 115°C at 0.05 mm Hg; 124°C at 0.06 mm Hg; IR 3610, 3400, 1650, 1600 $cm^{-1}$)

3-Methyl-6-phenylhex-5-en-2-one oxime (95% yield; IR 3620, 1645, 1600 $cm^{-1}$)

A mixture of 7-methyloct-6-en-3-one oxime and 3,6-dimethylhept-5-en-2-one oximes (98% yield, ratio 4:1; IR 3590, 3250, 1650, 1610, 1350 $cm^{-1}$)

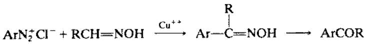
A mixture of 1-methoxy-8-methylnon-7-en-4-one oxime and 6-methyl-3-(2-methoxyethyl)hept-5-en-2-one oxime (yield 74%; IR 3300, 3120, 1652, 1450, 1380, 1127 $cm^{-1}$)

A mixture of ethyl 4-oxo-8-methylnon-7-enoate-4-oxime and 6-methyl-3-[(ethoxycarbonyl)methyl] hept-5-en-2-one oxime (yield 68%) [55b].

### C. Arylation of Aldoximes with Diazonium Salts

The reaction of diazonium salts with aldoximes was discovered by Borsche [55s], and it seems to have neglected, although it is a novel route to the preparation of aromatic aldehydes and ketones. The process may be presented by Eqs. 11 and 12:

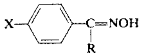
$$ArNH_2 \longrightarrow ArN_2^+\,Cl^- \qquad (11)$$



$$ArN_2^+Cl^- + RCH{=}NOH \xrightarrow{Cu^{++}} Ar{-}\overset{R}{\overset{|}{C}}{=}NOH \longrightarrow ArCOR \qquad (12)$$

A study of the scope of this reaction by Beech [55p] concerns itself with the preparation of the carbonyl compounds by this method, without describing the isolation of the intermediate arylated oximes.

The details of the preparation of oximes of the structure,



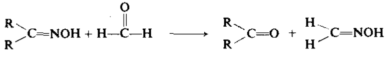
where X = Br, $COCH_3$, or $NO_2$, and R = H or $CH_3$ may have been given in a publication that was not available to us [55q].

The idea of preparing oximes from diazonium salts is intriguing and ought to be evaluated further both from the preparative standpoint and from the standpoint of the stereochemistry of the oximes produced by this method.

### D. Nitrosation of Active Methylene Compounds

The treatment of active methylene compounds such as ketones, β-keto esters, malonic esters, arylacetic esters, nitriles, aliphatic nitro compounds, and activated hydrocarbons with nitrosating agents such as nitrous acid or nitrite esters produces *C*-nitroso compounds which usually rearrange to oximino compounds [56–73a]. This reaction has been reviewed in great detail [56].

The reaction has value as a means of introducing an oximino function in a part of a molecule that does not have a carbonyl group for direct oximation. It also is an indirect means of introducing a new carbonyl group into a molecule. The oxime may then either be hydrolyzed under acidic conditions or be converted to a carbonyl by transoximation [57]. This latter procedure, as indicated in Eq. 13, merits further evaluation as a means of generating ketones from oximes.*



$$R_2C{=}NOH + H{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}H \longrightarrow R_2C{=}O + H_2C{=}NOH \qquad (13)$$

The oximino function may, of course, be prepared as an intermediate for the synthesis of amines. While the simple hydrolysis of oximino ketones to diketones does not always proceed satisfactorily, reductions to amino ketones seem to be invariably successful.

A large variety of nitrosating agents have been used with the various active methylene compounds. Thus, for example, nitrous acid may nitrosate simple aliphatic ketones like acetone, but may fail with other ketones. Nitrite esters, on the other hand, may react more satisfactorily in other cases. Several examples illustrating the various methods of nitrosation of active methylene compounds are given in Table III and Preparations 2-7, 2-8, and 2-9.

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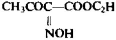
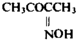
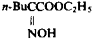
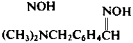
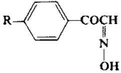
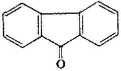
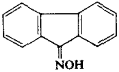
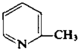
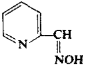
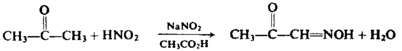
* Work on transoximation has shown that in the reaction of acetone oxime with α-keto aldehydes under reduced pressure or with acid catalysis, acetone and α-keto aldoximes are produced selectively [73b].

NITROSATION OF ACTIVE METHYLENE COMPOUNDS

| Active methylene compound (moles) | Nitrosation reagents (moles) | Acid or base (moles) | Solvent (ml) | Reaction conditions Temp. (°C) | Reaction conditions Time (hr) | Yield (%) | Structure of product | M.p. (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| $CH_3COCH_3$ (0.1) | $NaNO_2$ (0.218) | $CH_3COOH$ (30 ml) | — | 0 | 45 | 69 | $CH_3COCH{=}NOH$ | 65 | 58 |
| $CH_3COCH_2COOC_2H_5$ (5.8) | $NaNO_2$ (6.2) | $CH_3COOH$ (840 ml) | $H_2O$ (1000) | 25–35 | 1½–1 | 70–76 |  $CH_3CO\underset{\underset{NOH}{\Vert}}{C}{-}COOC_2H_5$ | 58–58.5 | 59 |
| $(HOCOCH_2)_2CO$ (0.103) | $NaNO_2$ (1.45) | — | $H_2O$ (475) | −5 to 0 | ½–1 | 51 | $(HON{=}CH)_2CO$ | 133d | 62 |
| $CH_3COC_2H_5$ (8.6) | $C_2H_5ONO$ (9.0) | conc. HCl (40 ml) | — | 40–45 | 1½ | 58 |  $CH_3CO\underset{\underset{NOH}{\Vert}}{C}CH_3$ | 76.5 | 21, 22 |
| $n$-BuCH$(COOC_2H_5)_2$ (0.3) | $C_2H_5ONO$ (0.4) | $C_2H_5ONa$ (0.3) | $C_2H_5OH$ (138) | −10 to 0 | 1½–2 | 80 |  $n\text{-Bu}\underset{\underset{NOH}{\Vert}}{C}COOC_2H_5$ | 53–55 | 66 |
| $(CH_3)_2NCH_2C_6H_4COCH_3$ (0.077) | $C_4H_9ONO$ (0.08) | $C_2H_5ONa$ (0.088) | $C_2H_5OH$ (100) | −10 to 0 | ½–1 | 98 |  $(CH_3)_2NCH_2C_6H_4\overset{\overset{NOH}{\Vert}}{C}H$<br> | 248–249 | 67 |
|  (1.0) | $C_4H_9ONO$ (1.07) | KOH (1.52) | $C_4H_9OH$ (500) | 100–120 | ½–1 | 73 |  | 187–188 | 68 |
|  (3.0) | $C_4H_9ONO$ (1.0) | Na (0.087) | $NH_3$ (400)<br>$(C_2H_5)_2O$ (100) | — | 1 | 75 |  | 113–113.5 | 71 |

### 2-7. *Preparation of Oximinoacetone (Isonitrosoacetone)* [58]

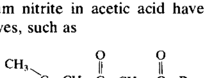


$$\mathrm{CH_3-\overset{\overset{O}{\|}}{C}-CH_3 + HNO_2 \xrightarrow[CH_3CO_2H]{NaNO_2} CH_3-\overset{\overset{O}{\|}}{C}-CH{=}NOH + H_2O} \qquad (14)$$

To a well-stirred, ice-cooled solution of 5.8 gm (0.1 mole) of acetone in 30 ml of glacial acetic acid is added dropwise a concentrated aqueous solution containing 15 gm of sodium nitrite. Stirring at 0°C is continued for 45 min, then 100 ml of water is added and the crude product is extracted with ether.

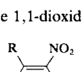
The ether extracts are combined, washed repeatedly with 10 ml portions of water, and dried with sodium sulfate. The ether is evaporated off under reduced pressure and the residue is dried on a porous plate. After recrystallization from benzene, 6 gm (69%) of the product is isolated, m.p. 65°C.

Ethyl acetoacetate has been converted to ethyl oximinoacetoacetate by a similar procedure [59]. Among other compounds converted to oximes by nitrosation with sodium nitrite in acetic acid have been diketones and malonic ester derivatives, such as



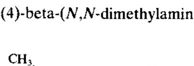
where R is $CH_3$, $C_6H_5$, or $OC_2H_5$ [73c];

3,5-Dihydro-3-nitrosothiophene 1,1-dioxides



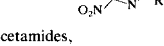
where R is hydrogen, $CH_3$, or Cl [73d];

enamines such as 5(4)-beta-(*N*,*N*-dimethylamino)ethylene-4-(5)-nitroimidazoles,



[73e];

and N,N-dialkylacetoacetamides,



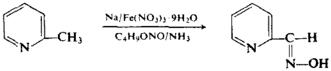
$$\mathrm{CH_3-\overset{\overset{O}{\|}}{C}-CH_2-\overset{\overset{O}{\|}}{C}-NR_2}$$

[73f]

Under basic conditions, malonic esters may be nitrosated [66]. This reaction is of particular interest since the oxime, on reduction, produces esters of $\alpha$-amino acids directly. Alternate procedures usually require the preparation of an $\alpha$-amino acid prior to esterification.

The preparation of 2-pyridine aldoxime is an extreme example of the use of basic conditions for the nitrosation of an active methylene compound.

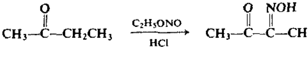
### 2-8. *Preparation of syn-2-Pyridine Aldoxime from 2-Picoline in Liquid Ammonia* [71]



(15)

In a hood, in a suitably coded flask equipped with an explosion-proof stirrer, a *Dry Ice-cooled reflux condenser, is placed 400 ml of anhydrous* liquid ammonia and 0.5 gm of ferric nitrate nonahydrate. To the flask is added, with vigorous stirring 46 gm (2.0 gm-atom) of sodium metal. The metal is permitted to dissolve completely and, after approximately 20 min, the blue color changes to gray. At this point, 279 gm (3 moles) of 2-picoline is added over a 30-min period. After stirring for 1 hr, a solution of 103 gm (1.0 mole) of butyl nitrite in 110 ml of diethyl ether is added over a 45-min period (intense red mixture forms). The reaction is quite rapid and considerable amounts of solids form. After 1 hr, a solution of 198 gm (1.5 moles) of ammonium sulfate in 300 ml of water is added rapidly. A thick precipitate of sodium sulfate replaces the solid previously formed and the color disappears. *While 500 ml of ether is being added, the ammonia is* allowed to evaporate. When the temperature has reached room temperature, the liquids are separated and filtered free of solids. The solids are washed repeatedly with ether. The ether layers are combined, the aqueous layer is separated, and repeatedly extracted with ether. The ether extracts are combined and distilled, first at atmospheric pressure, then at reduced pressures up to 80°C (2 mm) to remove butanol and unreacted reduced pressures up to 80°C (2 mmHg) to remove butanol and unreacted 2-*picoline*. Finally the product is distilled at 110°C (0.9 mm Hg) through a wide-diameter distillation head to afford 91.5 gm (75% base on requirement of 2 gm-atom of Na per mole of product), m.p. 105–111°C. On recrystallization from benzene, *the melting point is raised to 113–113.5°C.*

### 2-9. *Preparation of Biacetylmonoxime* [21, 22]



$$CH_3-\overset{O}{\overset{\|}{C}}-CH_2CH_3 \xrightarrow[HCl]{C_2H_5ONO} CH_3-\overset{O}{\overset{\|}{C}}-\overset{NOH}{\overset{\|}{C}}-CH_3$$

(16)

Approximately 9 moles of ethyl nitrite are required for this preparation. The literature indicates a suitable apparatus for its generation [44].

In a well-ventilated hood, to freshly dried and distilled methyl ethyl ketone (620 gm, 8.6 moles) is added, with stirring, 40 ml of conc. hydrochloric acid. The temperature of the reaction system is raised to 40°C. Without delay the addition of ethyl nitrite is initiated and the flow of the reagent is regulated to such a rate that the reaction temperature never exceeds 55°C. About 1.5 hr are required for the addition. The ethanol formed in the reaction, as well as unreacted methyl ethyl ketone, is separated by distillation until the pot temperature just reaches 90°C.

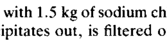
The product is separated from the residue by rapid steam distillation. Virtually all of the product will be found in the first 5 liters of the distillate. The distillate is saturated with 1.5 kg of sodium chloride and cooled to 0°C. The product, which precipitates out, is filtered off. If necessary, the product may be recrystallized from water to afford 500 gm (58%), m.p. 76.5°C.

Using methyl nitrite and hydrogen chloride, 2-oximino-1-phenyl-1-propanone (isonitrosopropiophenone), m.p. 112–113°C [64] and from phenacyl chloride, with *n*-butyl nitrite and hydrogen chloride, $\omega$-chloro-$\omega$-oximinoacetophenone, m.p. 132–133°C have been prepared [65].

Oximes were also prepared from a series of methylpyrimidines with isoamyl nitrite in liquid ammonia [72].

The oxime 16-oximinoandrost-5-en-3 $\beta$-ol-17-one has been prepared from dehydroisoandrosterone, using isoamyl nitrite with potassium *tert*-butoxide, in *tert*-butanol [73g].

A variety of acetoacetamides,



$$CH_3\overset{\overset{\displaystyle O}{\|}}{C}—CH_2—\overset{\overset{\displaystyle O}{\|}}{C}—NR^1R^2$$

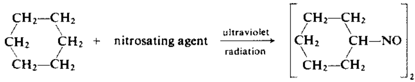
where $R^1$ is cyclohexyl, $C_6H_5$, $C_4H_9$, $C_8H_{17}$, cyclododecyl, and hexadecyl and $R^2$ is H, $CH_3—C_4H_9$, cyclohexyl or $NR^1R^2$ is pyrroldino, 1-piperidinyl, morpholino, and hexamethylenimino, have been converted to the 2-hydroximino derivative with isopropyl nitrite and HCl. The ketonic carbonyl was then treated with hydroxylamine hydrochloride and sodium acetate to prepare the dioxime [73h].

The 1-phenyl-1,2,3-butanetrione 2-oximes were prepared by the acid-catalyzed nitrosation of the corresponding beta-diketones with butyl nitrite in carbon tetrachloride. The effect of alkyl substituents on the stereoisomerization of the oximes was discussed. In some cases, the E- and Z-isomers were separated by medium-pressure chromatography on silica gel with hexane: acetone (ratio of 19:1) [73i].

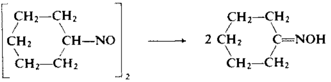
A nitrosating agent for active methylene compounds that may have industrial value is nitric oxide (NO). This is said to produce oximino ketones from ketones in the presence of air and catalytic amounts of aqueous hydrochloric acid [73a].

## E. Free-Radical *C*-Nitrosation of Saturated Hydrocarbons

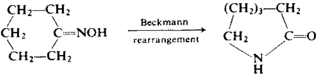
Victor Meyer's discovery of oximes [74] and research by others into such diverse fields of chemistry as cyclic aliphatic hydrocarbons, photochemistry, free-radical reactions of hydrocarbons, the isomerization of nitroso compounds, the Beckmann rearrangement, and the reactions of lactams led to a method of preparing polyamides of the Nylon 6 type as shown in Eqs. (17–20) [75].



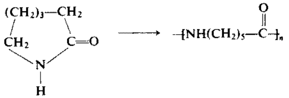
(17)



(18)



(19)



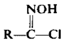
(20)

The photonitrosation and oximation of saturated hydrocarbons [76–95] has been reviewed by a research group which has worked in the field extensively [76]. The use of the reaction sequence given in Eqs. (17–20) has also been reviewed [77].

No detailed reaction procedures will be given since specialized equipment beyond the scope of the ordinary synthetic laboratory is required.

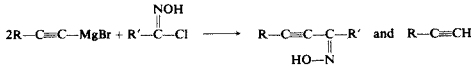
### F. Grignard Coupling Reaction

On treatment with chlorine or nitrosyl chloride, aldoximes can be converted to the corresponding hydroximic acid chlorides (hydroximyl chlorides) [96].



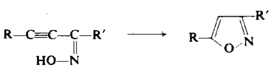
$$\mathrm{R{-}\overset{\overset{NOH}{\|}}{C}{-}Cl}$$

Recently this type of reagent has been reacted with acetylenic Grignard reagents to produce acetylenic ketoximes, uncontaminated with isoxazoles (Eq. 21) [97].



$$\mathrm{2R{-}C{\equiv}C{-}MgBr + R'{-}\overset{\overset{NOH}{\|}}{C}{-}Cl \longrightarrow R{-}C{\equiv}C{-}\underset{\underset{HO{-}N}{\|}}{C}{-}R' \text{ and } R{-}C{\equiv}CH} \tag{21}$$

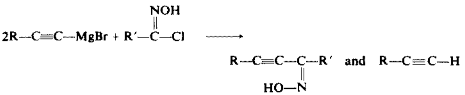
In the presence of base these oximes cyclize to isoxazoles (Eq. 22). At higher temperatures this cyclization also takes place. Even at room temperature this reaction takes place slowly. Therefore, the product must be stored in the refrigerator.



(22)

The configuration of these oximes appears to be *syn* with respect to the acetylenic bond.

### ***2-10. General Procedure for the Preparation of α,β-Acetylenic Ketoximes*** [97]



$$\mathrm{2R{-}C{\equiv}C{-}MgBr + R'{-}\overset{\overset{NOH}{\|}}{C}{-}Cl \longrightarrow R{-}C{\equiv}C{-}\underset{\underset{HO{-}N}{\|}}{C}{-}R' \text{ and } R{-}C{\equiv}C{-}H} \tag{23}$$

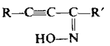
In a 1-liter three-necked flask equipped with a mechanical stirrer, a Dry Ice condenser, and an addition funnel is prepared a 0.2 mole solution of ethyl magnesium bromide in 300 ml of anhydrous ether by conventional procedures. With stirring, 0.2 mole of the required acetylene is added at such a rate that only a gentle reflux is observed. Stirring and warming (if necessary) is continued until an insoluble phase separates (2-3 hr).

Meanwhile, from the corresponding aldoxime, the required hydroximyl chloride is prepared and extracted into 250 ml of ether. The ether solution is dried for 5 min over anhydrous calcium chloride and another 5 min over Linde Type 4A molecular sieve pellets.

The dry ether solution of the hydroximyl chloride is added dropwise, with stirring, at 0°C over a 1-hr period to the Grignard reagent. After the addition has been completed, stirring is continued for an additional 10 min, then the reaction mixture is slowly and cautiously acidified with 200 ml of 10% sulfuric acid. The ether layer is separated. The aqueous layer is repeatedly extracted with ether. The ether layers are combined, washed with saturated sodium chloride solution, and dried with sodium sulfate. The ether is separated under reduced pressure using a rotary evaporator at room temperature. In some cases, pressures as low as 1 mm may be required to remove traces of ether. The solid products may finally be recrystallized from petroleum ether (b.p. 66–75°C). Table IV [97] lists the yields and melting points of 15 ketoximes prepared by essentially this procedure.

TABLE IV

PROPERTIES OF α,β-ACETYLENIC KETOXIMES[a]

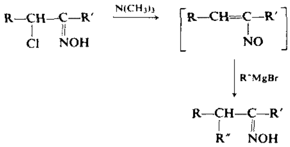


$$R{-}C{\equiv}C{-}\underset{\substack{\| \\ HO{-}N}}{C}{-}R'$$

| R = | R′ = | M.p. (°C) | Yield (%) |
|---|---|---|---|
| $CH_3$ | $(CH_3)_2CH$ | *Liquid* | 47 |
| $CH_3$ | $(CH_3)_3C$ | 81–82 | 68 |
| $CH_2{=}C(CH_3)$ | $CH_3$ | Liquid | 42 |
| $CH_2{=}C(CH_3)$ | $(CH_3)_3C$ | 47–48 | 57 |
| $C(CH_3)_3$ | $(CH_3)_2CH$ | Liquid | 65 |
| $C(CH_3)_3$ | $C(CH_3)_3$ | Liquid | 67 |
| $C(CH_3)_3$ | $CH_3CH_2CH(CH_3)$ | Liquid | 69 |
| $C_6H_5$ | $CH_3$ | Liquid | 35 |
| $C_6H_5$ | $CH_3CH_2$ | Liquid | 36 |
| $C_6H_5$ | $CH_3CH_2CH$ | Liquid | 45 |
| $C_6H_5$ | $(CH_3)_2CH$ | 89–90 | 61 |
| $C_6H_5$ | $CH_3CH_2CH(CH_3)$ | 82–83 | 51 |
| $C_6H_5$ | $C(CH_3)_3$ | 102–102 | 69 |
| $C_6H_5$ | $CH_3CH(C_6H_5)$ | 81–82 | 39 |
| $C_6H_5$ | $C_6H_5$ | 100–101 | 70 |

[a] From Hamlet *et al.* [97].

The α-chloro oximes have a reactive chloro group. On treatment with a tertiary amine, presumably, an α-olefinic nitroso compound may form (not isolated) which on reaction with Grignard reagents, produces branched oximes (Eq. 24) [98].

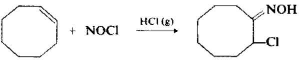


(24)

## 3. ADDITION REACTIONS

The formation of *C*-nitroso compounds upon addition of nitrosyl chloride or oxides of nitrogen to olefins has been discussed in Vol. II, Chapter 16, of this series. Conditions for the isomerization of nitroso compounds have been discussed. In general, if these additions are carried out in a medium which is saturated with hydrogen chloride, oximes are isolated. This approach makes the tacit assumption that nitrosyl chloride, rather than hydrogen chloride, will add to the double bond preferentially. An example of this procedure is given in Preparation 3-1. A recent reexamination of this addition reaction is reported in Shiue and Clapp [99].

***3-1. Preparation of 2-Chlorocyclooctanone Oxime* [100]**



(25)

In a well-ventilated hood, to a stirred solution of 22 gm (0.2 mole) of cyclooctene in 40 gm of cyclohexane which has been saturated with hydrogen chloride is added 13.1 gm (0.2 mole) of nitrosyl chloride while maintaining the reaction temperature between 15° and 30°C. Hydrogen chloride is added from time to time to keep the solution saturated with respect to hydrogen chloride. The 2-chlorocyclooctanone oxime hydrochloride separates. It is filtered off, washed with fresh cyclohexane, and dried in a vacuum desiccator. The dried hydrochloride is stirred with a small quantity of water. The free oxime, which first separates as an oil, crystallizes rapidly. It is filtered and dried to afford 30.2 gm (87%), m.p. 99°C. Upon recrystallization from petroleum ether, the melting point is raised to 102°C.

Another description of the preparation of the hydrochloride is found in Ohno et al. [101].

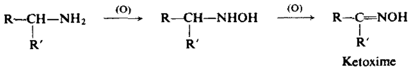
This method of forming oximes requires further development. In the case of the treatment of steroid 5-enes with an excess of nitrosyl chloride in methylene dichloride or in carbon tetrachloride, good yields of 5-$\alpha$-chloro-6-$\beta$-nitrosteroids are formed. Some of these, on reduction with chromous chloride in methanolic hydrochloric acid gave oximes such as 6-oximino-5 $\alpha$-methoxycholestan-3-$\beta$-ol acetate [73j].

## 4. OXIDATION REACTIONS

In Volume II, Chapter 16, of this series, a number of oxidative procedures are given for the oxidation of amines and hyroxylamines to C-nitroso compounds. When the carbon atom carrying the amino or hydroxylamino group is either primary or secondary, under conditions indicated in the previous section for the free-radical C-nitrosation of saturated hydrocarbons, the possibility of rearranging these oxidation products to oximes exists. However, these methods evidently are not always reliable for the preparation of oximes in optimum yields.

A method of oxidizing aliphatic, araliphatic, and alicyclic mono- and diamines with hydrogen peroxide in the presence of catalytic amounts of soluble salts of tungstic, molybdic, and uranic acid has been devised which makes use of relatively mild reaction conditions. This oxidation seems to involve the intermediate formation of hydroxylamines and may therefore be used for oxidation of hydroxylamines. As indicated in Eqs. (26 and 27) the substitution of the carbon bearing the amino group determines whether aldoximes or ketoximes are formed:

$$R{-}CH_2{-}NH_2 \xrightarrow{(O)} R{-}CH_2{-}NHOH \xrightarrow{(O)} \underset{\text{Aldoxime}}{R{-}CH{=}NOH} \tag{26}$$



$$R{-}\underset{\substack{|\\ R'}}{CH}{-}NH_2 \xrightarrow{(O)} R{-}\underset{\substack{|\\ R'}}{CH}{-}NHOH \xrightarrow{(O)} \underset{\text{Ketoxime}}{R{-}\underset{\substack{|\\ R'}}{C}{=}NOH} \tag{27}$$

Generally the yields of ketoximes tend to be higher than those of aldoximes, presumably because the aldoximes tend to be oxidized further to hydroxamic acids and possibly to free aldehydes. Table V [102] shows a large variety of oximes each of which was prepared directly from the corresponding amine. To be noted, for example, is that amino alcohols form oximino alcohols and diamines form dioximes. Other functional groups evidently also survive this mild oxidation [102a,b]. It was observed that many of the oximes formed addition complexes with the starting amines in equimolar proportion. These are crystalline materials of great insolubility. Such precipitates may be brought back into solution by the addition of monofunctional alcohols during the oxidation. However, in some cases it may be advantageous to isolate this complex and convert it to the oxime by thermal degradation during distillation. The preparation of butyraldoxime is representative of one of the reaction procedures.

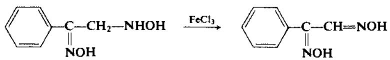
### *4-1. Preparation of Butyraldoxime* [102a]

$$CH_3CH_2CH_2CH_2NH_2 \xrightarrow{(O)} CH_3CH_2CH_2CH{=}NOH \qquad (28)$$

To a slowly stirred mixture of 73 gm (1 mole) of butylamine and 109 gm of a 12.2% aqueous solution of sodium tungstate is added (1¾ hr) with cooling to maintain a temperature of 15°C, 220 gm of 28% hydrogen peroxide. During this reaction 130 ml of ethanol is added portionwise to clarify the emulsion which tends to form. The green solution is stirred at 15°C for an additional hour after the addition has been completed. The reaction mixture is cooled, neutralized, and freed of the ethanol under reduced pressure. The solution is then saturated with sodium chloride and the oily product is separated and distilled to afford 50 gm (58%), b.p. 152°C. Several other examples of this procedure are given in Table V.

Evidently hydroxylamines may also be oxidized with hydrogen peroxide in the presence of sodium tungstate, as mentioned above. In a recent report, phenylglyoxime was prepared by a ferric chloride oxidation of the correspondingly hydroxylamine oxime [103].

### *4-2. Preparation of Phenylglyoxime by Oxidation of a Hydroxylamine Derivative* [103]



(29)

To a solution of 1.66 gm (0.01 mole) of $\alpha$-hydroxylaminoacetophenone oxime is added a solution of 2.71 gm (0.01 mole) of ferric chloride hexahydrate in 100 ml of ethanol. The mixture is filtered and the filtrate is evaporated. The resultant dark oil is dissolved in a 1:1 (v:v) solution of methylene chloride–ether, washed with a saturated aqueous ammonium chloride solution, and dried with sodium sulfate. After filtration, the solvent is evaporated off. The residue is recrystallized from ether–hexane

TABLE V

Oximes Prepared by Oxidation of Amines[a]

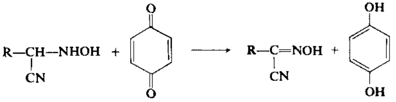
| Oxime | B.p., °C (mm Hg) | M.p. (°C) |
|---|---|---|
| *n*-Butyraldoxime | 152 | — |
| *n*-Propionaldoxime | 132 | — |
| Acetonoxime | — | 60 |
| Acetaldoxime | — | 46 |
| Hexanedialdoxime | — | 168 |
| Glyoxime | — | 175 |
| Cyclohexanone oxime | — | 90 |
| 2-Methylcyclohexanone oxime | — | 41 |
| Bis(4-oximinocyclohexyl)methane | — | 203 |
| Benzaldoxime | — | 34.5 |
| Terephthaldoxime | — | 194 |
| 4-Ethoxycyclohexanone oxime | 108–111 (5) | — |
| 4-Hydroxycyclohexanone oxime | 161–164 (11) | — |
| 2-Methylolcyclohexanone oxime | — | 87 |
| 4-Carbethoxycylohexanone oxime | 166 (11) | — |
| *p*-Carboxybenzaldoxime | — | 208 |
| ε-Oximinocaproamide | — | 154 |
| Ethyl ε-oximinocaproate | 149–152 (11) | — |
| Ethyl α-oximinopropionate | — | 96–97 |
| Glycolaldoxime | — | 48–50 (gradually decomposes in air) |

[a] From Kahr and Berther [102a] and Kahr [102b].

*to afford 0.4 gm (25%), m.p. 147°C.* This melting point appears to be rather low even for a mixture of the three isomers (see section 2).

Benzoquinone has been used as an oxidizing agent of α-hydroxylaminonitriles. During this dehydrogenation, the quinone is first converted to quinhydrone and finally to hydroquinone. Procedure 4-3 is a generalized version of this method [104].

### ***4-3. General Procedure for the Oxidation of α-Hydroxylaminonitriles with Benzoquinone*** **[104]**

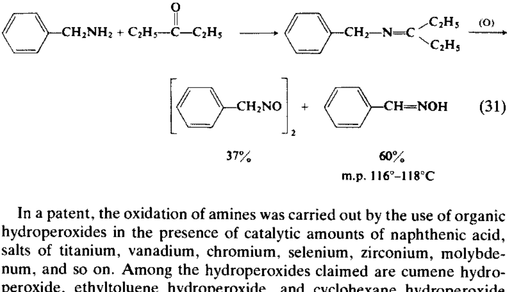


(30)

To a suspension of 0.1 mole of an α-hydroxylaminonitrile in 500 ml of benzene is added, with shaking, 0.1 mole of benzoquinone. After the addition has been completed, the reaction mixture is refluxed on a steam bath for 3–5 hr. During this time, crystals of quinhydrone form which are gradually converted to hydroquinone. The reaction mixture is cooled, filtered, and evaporated under reduced pressure. The product ia separated from the hydroquinone by treating the residue with carbon tetrachloride or carbon tetrachloride–benzene mixture, depending on the solubility. After filtration, the filtrate is evaporated under reduced pressure and the final product is purified by molecular distillation. The prodcuts are colorless oils, yields range between 40 and 65%.

By this procedure the following oximinonitriles were prepared: α-oximinopropionitrile, b.p. 35°C (0.9 mm Hg), $n_D^{25}$ 1.4542; α-oximinobutyronitrile, b.p. 42°C (1 mm Hg), $n_D^{25}$ 1.4528; α-oximinovaleronitrile, b.p. 32°C (0.03 mm Hg), $n_D^{25}$ 1.4531.

It will also be recalled (see Vol. 2, Chapter 16, of this series) that nitosoalkane dimers are readily prepared by the oxidation of oxaziranes or imines [105a]. While these dimers may be isomerized to oximes, with one exception, no significant amounts the oximes could be isolated from the reaction mixture–evidently the rate of formation of the stable *C*-nitrosoalkane dimers is more rapid than the rate of tautomerization. The exceptional case is represented by Eq. (31) in which the major product consisted primarily of benzaldoxime.



(31)

In a patent, the oxidation of amines was carried out by the use of organic hydroperoxides in the presence of catalytic amounts of naphthenic acid, salts of titanium, vanadium, chromium, selenium, zirconium, molybdenum, and so on. Among the hydroperoxides claimed are cumene hydroperoxide, ethyltoluene hydroperoxide, and cyclohexane hydroperoxide [105b].

On an industrial scale, oximes have been prepared by ammoximation of cyclohexanone with ammonia and oxygen [105c–e]. In the presence of a catalyst such as titanium silicate, ammoximations may be carried out using hydrogen peroxide as the oxidizing agent [105f].

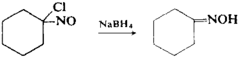
## 5. REDUCTION REACTIONS

Only a limited number of reductive procedures have been suggested as means of producing oximes. Essentially these involve reductions of *gem*-chloronitroso compounds, reductions of nitroalkanes and nitroolefins, and the reduction of furoxans (furazan-1-oxides).

The reduction of *gem*-chloronitroso compounds is of some importance since these intermediates are formed on free-radical nitrosations of cyclohexane in the presence of chlorine and by some nitrosations involving nitrosyl chloride.

While these intermediates have been reduced by catalytic hydrogenation and with lithium aluminum hydride [8], the use of sodium borohydride seems preferable for a laboratory procedure both in terms of yield and safety. As we have recommended elsewhere, a small amount of potassium hydroxide should be added to the initial reaction mixture to stabilize the reducing agent. It also should not be assumed that the borohydride reduction is instantaneous even though the reaction is followed by the change in color as the reducing agent is being added. We suggest that the effect on yield of prolonged standing prior to work up be evaluated.

### *5-1. Preparation of Cyclohexanone Oxime* [81a]



(32)

To a cooled, well-stirred solution of 2 gm (0.0115 mole) of 1-chloro-1-nitrosocyclohexane dissolved in a mixture of 20 ml of ethanol and 10 ml of distilled water is added, in small increments, enough sodium borohydride until the color has been discharged. The reaction mixture, which is neutral, is acidified slightly to pH 4. The product is separated by exhaustive extraction with ether. The ether extract is dried over sodium sulfate, filtered, and freed of ether by evaporation. The colorless crystal mass is pressed dry on a clay plate and recrystallized from petroleum ether to afford 0.94 gm (61%), m.p. 89–90°C.

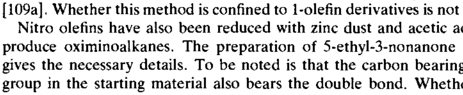
The partial reduction of aliphatic nitro compounds was mentioned as early as the turn of this century. However, only with the commercialization of nitroalkanes did these reactions achieve any real significance. Among the chemical reducing agents, zinc dust and acetic acid have been recommended [106, 107].

Hydrogenation of nitrocyclohexane on a silver dichromate catalyst has recently been patented [108]. In this procedure, it is said to be important to control the hydrogen take-up to prevent hydrogenation of the oxime to the hydroxylamine. This is accomplished by venting hydrogen off as soon as the theoretical quantity of hydrogen has been used up to convert the nitro compound to the oxime.

Olefinic nitro compounds have been reduced to the saturated oxime with hydrogen and a palladium-on-carbon catalyst. To maximize the yield of oxime, 0.5–1.0 mole of hydrogen chloride per mole of nitroolefin must be present. Since the by-products contain crude ketones also, a posttreatment with hydroxylamine hydrochloride and sodium acetate has been recommended [109a,b]. By this means, 1-nitrocyclooctene has been converted to cyclooctanone oxime [b.p. 63°C (0.08 mm Hg), m.p. 41.7–42.7°C] and 1-nitro-1-octadecene has been converted to stearaldoxime (m.p. 88–89.8°C) [109a]. Whether this method is confined to 1-olefin derivatives is not clear.

Nitro olefins have also been reduced with zinc dust and acetic acid, to produce oximinoalkanes. The preparation of 5-ethyl-3-nonanone oxime gives the necessary details. To be noted is that the carbon bearing nitro group in the starting material also bears the double bond. Whether this structural feature is essential if the reduction is to stop at the oxime stage may need further elucidation.

### *5-2. Preparation of 5-Ethyl-3-nonanone Oxime* [110]



$$CH_3(CH_2)_3{-}\underset{C_2H_5}{\underset{|}{CH}}{-}CH{=}\underset{NO_2}{\underset{|}{C}}{-}CH_2CH_3 \xrightarrow[CH_3CO_2H]{\text{Zn dust}} CH_3(CH_2)_3{-}\underset{C_2H_5}{\underset{|}{CH}}{-}CH_2{-}\underset{NOH}{\underset{\|}{C}}{-}CH_2CH_3 \qquad (33)$$

In a three-necked, conical flask fitted with a mechanical stirrer, dropping funnel, and reflux condenser, to 50 gm (0.88 gm-atom) of zinc dust and a solution of 43 gm (0.22 mole) of 3-nitro-5-ethyl-3-nonene in 200 ml of ether is added with vigorous stirring over a 2–4 hr period 110 gm (0.46 mole) of a 25% aqueous acetic acid solution at such a rate that the ether refluxes gently. After the addition has been completed, the reaction mixture is warmed until it becomes colorless and no more hydrogen evolves (4–6 hr). After filtration of the zinc acetate, and exhaustive extraction of the zinc acetate in a Soxhlet extractor with ether, the ether solutions are combined and concentrated on a water bath. The excess acetic acid is separated at low pressure and the residue is distilled to afford 71 gm (52%), b.p. 89–92°C (1 mm Hg). The product is a viscous oil of strong

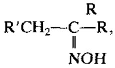
TABLE VI

PROPERTIES OF KETOXIMES PREPARED BY THE ZINC/ACETIC ACID REDUCTION OF NITROOLEFINS[a]

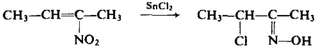
| Ketoxime of | B.p., °C (mm Hg) | $n_D^{25}$ |
|---|---|---|
| 5-Ethyl-3-heptanone | 75–79 (1) | 1.4547 |
| 3-Decanone | 81 (1) | 1.4532 |
| 5-Ethyl-3-nonanone | 89–92 (1) | 1.4560 |
| 4-Ethyl-2-hexanone | 69 (1) | 1.4522 |
| 5-Methyl-3-hexanone | 55 (1) | 1.4528 |
| 3-Heptanone | 56 (1) | 1.4522 |
| 3-Nonanone | 70 (1) | 1.4522 |
| 4-Ethyl-2-octanone | 81 (1) | 1.4534 |

[a] Data from D. Nightingale and J. R. Janes, *J. Amer. Chem. Soc.* **66**, 352 (1944).

odor. Table VI [110] gives the properties of a series of ketoximes prepared by this method.

Nitro olefins upon reduction with stannous chloride produce chlorooximino compounds in reasonable yields. Since this chlorosubstituent is $\alpha$ to the oximino group, it may be expected to be reactive and, indeed it will react with piperidine, for example, to give piperidino derivatives [111a]. Other nitroalkenes, such as $R'CH{=}C{-}NO_2$ have been reduced with stannous chloride to form  $R'CH_2{-}\overset{R}{\underset{\underset{NOH}{\|}}{C}}{-}R$, where R is H, $CH_3$; and R′ is $C_6H_5$, $4\text{-}BrC_6H_4$; $3,4\text{-}(C_2H_5O)_2C_6H_3$; and 1-naphthyl [111b].

### *5-3. Preparation of 2-Chloro-3-oximinobutane* [111a]


(34)

$$CH_3{-}CH{=}\underset{\underset{NO_2}{|}}{C}{-}CH_3 \xrightarrow{SnCl_2} CH_3{-}\underset{\underset{Cl}{|}}{CH}{-}\underset{\underset{N-OH}{\|}}{C}{-}CH_3 \qquad (34)$$

(*a*) *General procedure.* The required quantity of crystalline stannous chloride dihydrate is dried for several days in a vacuum desiccator over conc. sulfuric acid, whereupon the salt loses approximately 40% of its water content.

To ordinary ether which contains 1.5 mole of hydrogen chloride per mole of stannous chloride is added the requisite quantity of dried stannous chloride.

To a rapidly stirred solution of the nitroolefin in ether which also contains hydrogen chloride, the stannous chloride solution is added dropwise with cooling in an ice-salt bath. After the addition has been completed, stirring is continued for 2 hr. The reaction mixture is then extracted in turn with water, three times with dilute hydrochloric acid, once with a solution of tartaric acid, and finally five times with water. The ethereal solution is dried with sodium sulfate, the ether is evaporated, and the residue is either distilled or recrystallized to produce the purified chlorooxime.

(*b*) *2-Chloro-3-oximinobutane.* A solution of 50.5 gm (0.5 mole) of 2-nitro-2-butene and 27 gm of hydrogen chloride in 250 ml of ether is reduced over a 4 hr period with a solution of 157 gm (0.7 mole) of stannous chloride and 40 gm of hydrogen chloride in 750 ml of ether. The yield is 29 gm (48%), b.p. 79°C (11 mm Hg).

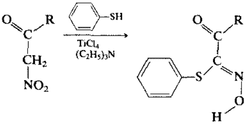
Other products produced by Procedure 5-3 were 1-chloro-2-oximinobutane, b.p. 85°C (13 mm Hg); 4-chloro-3-oximino-heptane, b.p. 75–76°C (0.3 mm Hg); α-chloropropionaldoxime, b.p. 78–79°C (11 mm Hg); 2-chloro-1-oximino-3-ethylpentane, b.p. 64°C (0.2 mm); 1-chloro-2-oximino 1-phenyl-propane, m.p. 87–89°C; and 1,1,1,2-tetrachloro-3-oximino-butane, b.p. 68°C (0.9 mm Hg).

The reduction of chloronitro compounds with chromous chloride was mentioned previously [73j]. Aliphatic nitro compounds have been reduced by zinc dust in acetic acid [107]. Alpha, beta-unsaturated beta-arylnitroalkenes have been reduced with chromous chloride [111c]. Another reducing agent for the production of alpha, beta-unsaturated oximes from the corresponding nitroalkene is sodium stannite [111d].

Carbon monoxide has been used for the selective reduction of nonaromatic nitro compounds. The reaction is carried out in an aqueous solution of a copper(I) acetate complex with 1,3-propandiamine. By this means, nitrocyclohexane was reduced to cyclohexanone oxime in 81% yield (m.p. 90°C), and a mixture of nitrododecane was converted to dodecanone oxime (as a mixture of isomers) (b.p. 126–128°C at 4 mm Hg). Because of the hazards of handling and disposing of carbon monoxide and of copper–amine complexes, we are not giving details of the procedure [111e].

Oximes of alkyl arylketones have been produced by the reaction of aryl-substituted olefins with nitric oxide (NO) in the presence of cobalt complexes and tetrahydroborate ions [111f].

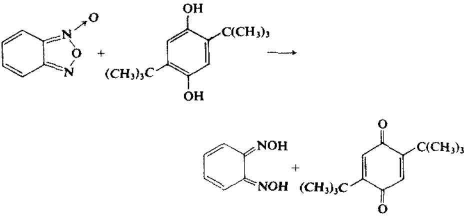
In the presence of thiophenol, titanium tetrachloride, and triethylamine, alpha-nitro ketones have been converted in a one-step process to alpha-acyl alpha-phenylthiooximes. The process is thought to be a nucleophilic dehydration:



(35)

where R = $C_6H_5$, $C_2H_5$, or $CH_3$ [111g]

Incidental to a one-step synthesis of quinoxaline 1,4-dioxides, a novel reduction of benzofurazan 1-oxide with 2,5-di-*t*-butylhydroquinone was mentioned [112]. Equation (36) indicates the reaction scheme. Extension of this reduction to other furoxan derivatives would be quite interesting.



(36)

## 6. ISOMERIZATION REACTIONS

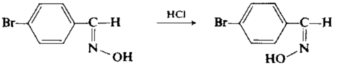
### A. *syn-anti* Isomer Formation and Separation

As has already been indicated, the oximes produced by many of the procedures given in this chapter are mixtures of *syn* and *anti* isomers unless specific structural features favor the formation of one isomer over the other. The separation of the geometric isomers is often possible by careful fractional crystallization, since the solubility of the two isomers is sufficiently different. In the older literature, the isomers were designated $\alpha$ and $\beta$ depending on this solubility difference. In the light of the confusion that exists in the nomenclature of oximes, caution must be exercised in assigning structures to the two forms.

The two isomers of *p*-chlorobenzophenone oxime were separated by fractional crystallization. The *syn-p*-chlorobenzophenone oxime crystallized from an 80% ethanol-20% water solution (m.p. 159.3–159.8°C), the *anti-p*-chlorobenzophenone was isolated by evaporating the mother liquor to dryness (m.p. 102.4–103.5°C) [113]. The isomers have also been separated by column chromatography on a silica gel column [114].

The *anti* isomer is sometimes produced from the *syn* form by treatment of a solution of the latter with hydrogen chloride. This technique is particularly applicable to aldoximes [115, 116]. It is suggested that the paper by Brady and Dunn [117] be reviewed in connection with this type of isomerization since it discusses points of technique in handling the intermediate hydrochloride salts. The reader must be cautioned, however, that the configurational assignments in Brady and Dunn [117] are probably incorrect in the light of current thinking on these structures.

### *6-1. Preparation of* anti-p-*Bromobenzaldoxime by Isomerization of* syn-p-*Bromobenzaldoxime* [115]

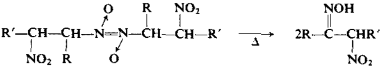


(37)

In a hood, anhydrous hydrogen chloride is passed through a stirred ether solution of 4.0 gm (0.02 moles) of *syn-p*-bromobenzaldoxime for 15 min. The less soluble hydrochloride salt of the *anti* isomer precipitated. After filtration of the product and washing with ether, the intermediate is dissolved in water. The solution is treated with a 2 *N* solution of sodium hydroxide until the mixture reaches pH 9. The precipitating product is collected on a filter and washed with cold water to afford 3.1 gm (78%), m.p. 134–135°C. Thin-layer chromatography using chloroform-ethyl acetate (4:1) shows a single spot with smaller mobility than that of the original *syn* isomer. The NMR (DMSO-$d_6$) are 7.46 pp. (s, 1, HC=N), 7.63 (d, $J = 9$ Hz, 2, Ar), 7.97 (d), $J = 9$ Hz, 2, Ar), 11.82 (s, 1, OH).

## B. *C*-Nitroso to Oxime Isomerization

The general problems and procedures of isomerization of *C*-nitroso compounds to oximes have been discussed in Section 2,C on the free-radical nitrosation of hydrocarbons. Another example of this rearrangement from the recent literature involves the thermal rearrangement of pseudonitrosites (2-nitronitroso dimers) to α-nitrooximes [103, 118] (Eq. 38).



$$\mathrm{R'{-}\underset{NO_2}{CH}{-}\underset{R}{CH}{-}\overset{O}{N}{=}\underset{O}{N}{-}\overset{R}{CH}{-}\overset{NO_2}{CH}{-}R'} \xrightarrow[\Delta]{} \mathrm{2R{-}\overset{NOH}{\overset{\|}{C}}{-}\underset{NO_2}{CHR'}} \qquad (38)$$

As is usual in the isomerization of nitroso compounds, here too, the fact that a hydrogen is attached to the carbon bearing the nitroso group facilitates the tautomerism to the oxime form.

## 7. PROPERTIES OF OXIMES

To demonstrate the variety of oximes which have been prepared by the methods outlined in this chapter, a series of tables listing some properties of these oximes is given in this section (Tables VII–XII). These tables are not meant to be exhaustive and are to be considered only supplementary to the tables of melting points of oximes found in the standard works on the identification of organic compounds.

TABLE VII

Properties of Substituted Benzaldoximes[a]

| Substituent | Configuration[b] | M.p. (°C) |
|---|---|---|
| H | *syn* | 35 |
| | *anti* | 132 |
| *p*-Methoxy | *syn* | 64 |
| | *anti* | 131.5 |
| 3,4-Methylenedioxy | *syn* | 111 |
| | *anti* | 146 |
| *m*-Nitro | *syn* | 120 |
| | *anti* | 123 |
| 3,4-Dimethoxy | *anti* | 119 |
| *o*-Methoxy | *syn* | 92–94 |

[a] From Brady and Dunn [117].

[b] The configurational assignments given here are exactly opposite to those of the original authors and are believed to be in line with current thinking.

## TABLE VIII

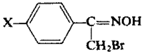
### Properties of α-Oximinoarylacetonitriles[a]

| A | Configuration | M.p. (°C) |
|---|---|---|
| Phenyl | *anti* | 129 |
| | *syn* | 97 |
| 4-Chlorophenyl | *anti* | 112 |
| | *syn* | 123 |

[a] From Stevens [114].

## TABLE IX

### Properties of *p*-Substituted 2-Bromoacetophenone Oximes[a]

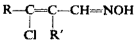


| X = | M.p., °C |
|---|---|
| H | 98–99 |
| $CH_3O$ | 101–102.5 |
| $CH_3$ | 117–118.5 |
| Cl | 118.5–119 |
| $NO_2$ | 129–129.5 |

[a] From Masaki *et al.* [119].

## TABLE X

### Properties of Aliphatic β-Chlorovinyl Aldoximes[a]



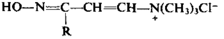
$$R{-}\underset{\displaystyle Cl}{C}{=}\underset{\displaystyle R'}{C}{-}CH{=}NOH$$

| R = | R′ = | M.p. (°C) |
|---|---|---|
| $CH_3$ | $CH_3$ | 118–119 |
| $C_2H_5$ | $CH_3$ | 75–75.5 |
| $-(CH_2)_3-$ | | 117.5–118 |
| $-(CH_2)_4-$ | | 108–108.5 |
| $-(CH_2)_5$ | | 37–40 |
| $-(CH_2)_6-$ | | 83.5–84.5 |

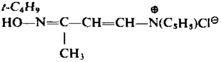
[a] From Benson and Pohland [120].

TABLE XI

Properties of $\beta$-Trialkylammonium Vinyl Ketoxime Chlorides[a]



$$HO{-}N{=}\underset{\displaystyle R}{\underset{|}{C}}{-}CH{=}CH{-}\overset{+}{N}(CH_3)_3Cl^-$$

| R = | M.p. (°C) |
|---|---|
| $CH_3$ | 190–195 (dec.) |
| $C_2H_5$ | 182–185 (dec.) |
| $i$-$C_3H_7$ | 165–170 (dec.) |
| $t$-$C_4H_9$ | 218 (dec.) |
|  $HO{-}N{=}\underset{\displaystyle CH_3}{\underset{|}{C}}{-}CH{=}CH{-}\overset{\oplus}{N}(C_5H_5)Cl^{\ominus}$ | 171–173 (dec.) |

[a] From Benson and Pohland [121].

TABLE XII

Miscellaneous Oximes

| Compound | M.p. (°C) | Ref. |
|---|---|---|
| 2,6-Dimethoxynaphthalene 1-aldoxime | 160–163 | 122 |
| 5-Bromo-2,6-dimethoxynaphthalene 1-aldoxime | 217–220 (dec.) | 122 |
| 2,4,6-Trimethylisophthaldialdoxime | 148–149 | 122 |
| 2-Dimethylamino-4,6-dichloropyrimidine-5-aldoxime | 165 | 122 |
| 4-Heptanone oxime | b.p. 65°–65.5°C (10)<br>($n_D^{28}$ 1.4468) | 123 |
| 1,3-Diphenyl-2-propanone oxime | 119–122 | 123 |
| Deoxybenzoin oxime (*syn*-benzyl isomer) | 94–96 | 123 |

## 8. MISCELLANEOUS METHODS

(1) Preparation of *O*-cyanoethylated oximes by reaction of oximes with acrylonitrile [123b].

(2) Preparation of *O*-allyl ethers of oximes by reaction of oximes with allyl bromide in the presence of sodium ethylate [123c].

(3) *O*-alkylation of oximes with epoxides [123d].

(4) *O*-alkylation versus *N*-alkylation of oximes, effected by the reaction medium, the leaving group, the cation, and so on [123e].

(5) Formation of azolylethyl oximinoalkyl ethers [123f].

(6) *O*-alkylation of oximes with 2-(bromomethyl)-1,3-dioxolane [123g].

(7) Preparation of *O*-alkylated oximes by reaction of a ketone with *O*-alkylated hydroxylamine [123h].

(8) Preparation of *O*-allyl ethers of oximes by reaction of carbonyl compounds with *O*-allylhydroxylamine hydrochloride in ethanol with anhydrous sodium acetate and anhydrous sodium carbonate [123i].

(9) The synthesis and reactions of alpha-hydroxylamino-oximes, a review covering the synthesis, properties, and reactions of α-hydroxylamino-oximes [123j]. (See also item 44 [152].)

(10) Preparation of amidoximes [123k].

(11) Condensation of halo ketone compounds with hydroxylamine [124].

(12) Addition of nitrosyl chloride or nitrosyl sulfuric acid to olefins [125].

(13) Pyrolysis of 2-*t*-butyl oxazirane derivatives [126].

(14) Condensation of benzonitrile oxide with a phosphonium ylide [127].

(15) Reaction of halo oximes with substituted phosphines [127].

(16) Reaction of α-chloropicoline with hydroxylamine [128].

(17) Reaction of methylolpyridine derivatives with hydroxylamine in the presence of phenylsulfene [129].

(18) Photoaddition of *N*-nitrosodialkylamines to cycloolefins [130].

(19) Diels-Alder reactions with chloronitrosocyclopentadienes [131].

(20) Preparation of oximinosilanes, oximinogermanes, and oximinostannanes [132a].

(21) Production of alkoxyoximinosilanes [132b].

(22) Silyloximation of ketones [132c].

(23) Preparation of α-oximinocarbonyl compounds by addition of nitrosyl chloride to trimethylsilyl enol ethers [132d].

(24) Preparation of organo *N*-hydroxyimidates [132e].

(25) Preparation and use of oximinophosphoric acid derivatives [132f].

(26) Reaction of *N*-(2-oximinocyclohexyl)pyridinium chloride with primary and secondary amines, a novel derivatizing reagent [133].

(27) Rearrangement of *N*-nitrosoaminoacetonitriles [134].

(28) Preparations from furoxans [135, 136].

(29) α-Oximation of saturated ketones with photochemically excited nitrite ions [137].

(30) Friedel–Crafts type reaction of fulminic acid with aromatic hydrocarbons [138].

(31) Reaction of alkyl halides with *O*-acetylbenzenesulfonhydroxamic acid salts (*O*-acetyl derivatives of "Piloty's acid") [139].

(32) Thermal decomposition of lithium salts of *O*-diphenylmethylhydroxylamine-*N*-*p*-toluenesulfonamides (O to N migration) [140].

(33) Reaction of nitrile oxides and acylacetylenes to afford isoxazoles and oximes [141]. (NOTE: The products are said to form by separate mechanisms. Therefore it may be of interest to study conditions required to maximize the yield of one or the other of the products.)

(34) Electrophilic substitution of enamies with nitrosyl chloride [142].

(35) Cope-type reaction of nitro nitrones [143].

(36) Intramolecular addition to a carbon-carbon double bond upon photolysis of organic nitrites [144].

(37) Reaction of benzonitrile oxide with aziridine derivatives and aziridine precursors [145].

(38) Ring opening of pyrroles with hydroxylamine [146].

(39) Ring opening of dihydropyridines with hydroxylamine [147].

(40) Ring opening of 1,2-oxazoles with base [148].

(41) Ring opening of furazans with base [149].

(42) Aldoximes: an extensive review of the chemistry of amidoximes and related compounds will be found in Eloy and Lenaers [150].

(43) Preparation of arylazo oximes [151].

(44) Preparation of primary $\alpha$-hydroxylaminooximes [152]. (See also item 9, [123j].)

(45) Treatment of nitro esters with sulfuric acid [153].

(46) Reduction of trihalonitrosomethane with hydrogen sulfide [154a, b].

(47) Chlorination of 1-chloro-1-hydroxyliminoacetone [155].

(48) Formation of phenacyl bromide oxime from phenacyl bromide and hydroxylamine [156].

(49) Preparation of pyridine-2-aldoximes by the reaction of 2-methylpyridines with iodine-DMSO and subsequent reaction with hydroxylamine [49].

(50) Preparation of alkoxyiminoalkyl bromides by the NBS bromination of *O*-alkyl oximes [157].

(51) Preparation of optically active $\alpha$-oximino ketones [158].

(52) Preparation of $\alpha$-methylene oximes [159].

(53) Selective transoximation of $\alpha$-keto aldehydes with acetone oxime to form $\alpha$-keto aldoximes under reduced pressure or acidic conditions [73b].

(54) Reaction of alkyl trialkoxysilanes and ketoximes to form silylated ketoximes [160].

(55) Regiospecific ketoxime synthesis by reaction of an alkyl nitrite and aryl-substituted ethylenes using cobalt complexes and $BH_4^-$ as catalyst [161].

(56) Conversion of ketoximes to ketones by a mild reductive procedure [162].

(57) A mild and selective procedure using a quaternary ammonium permanganate to generate carbonyl compounds from oximes and (2,4-dinitrophenyl)-hydrazones [163].

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# CHAPTER 12/HYDROXAMIC ACIDS

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## 1. INTRODUCTION

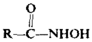
Although hydroxamic acids have been known for over a century [1] and a considerable body of literature exists on the subject, the study of their chemistry and practical applications has lagged until quite recently. Exner, whose contribution to the field cannot be overestimated, states that it was probably the uncertainty of the structure of hydroxamic acids which prevented further development of their chemistry [2].

Thus, for example, while the *Chemical Abstracts* guide to naming and indexing in 1962 mentions on one page [3] that both tautomeric forms of the hydroxamic acids are to be named "hydroxamic acids," and the displayed example gives $C_6H_5C(:NOH)OH$ as the formula for benzohydroxamic acid. On another page [4], the more commonly acceptable formula for benzohydroxamic acid was given, without comment about possible tautomerism, as $C_6H_5CONHOH$. We mention this matter here only as an example of the confusion that exists in the literature.

The *1982–1986 Chemical Abstracts Index Guide* does list "Hydroxamic Acids," but it does not display any structures for our guidance.

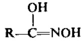
The increasing interest in hydroxamic acids has been attributed, in part, to work on cycloserine (D-4-amino-3-isoxazolidone, "oxamycin") [5], ferrichromes [6], work on the acceleration of hydrolysis of organic fluorophosphates and fluorophosphonates, such as the nerve gas Sarin (isopropyl methylphosphono-fluoridate) by hydroxamic acids [7], various analytical applications (based either on the characteristic color formed on reaction of hydroxamic acids with ferric chloride solution or their ability to act as chelating agents), uses as floatation agents (again, related to their chelating abilities), and biochemical or medicinal studies. Polymeric hydroxamic acids have received some attention as ion-exchange resins, particularly for the extraction of metals from aqueous media by chelation.

A number of review articles deal with the chemistry of hydroxamic acids. One of the earliest is by Lossen [8], which summarizes the status of approximately twenty-five years of research both by himself and his coworkers and others. It is interesting to note that as of the time of that review, Lossen still had reservations about the concept of restricted rotation about double bonds. He did not accept the stereochemical concepts proposed by Werner [9], who carefully differentiated between hydroxamic acids



$$\mathrm{R{-}\overset{\overset{O}{\|}}{C}{-}NHOH}$$

and their tautomers, the hydroximic acids,



$$\mathrm{R{-}\overset{\overset{OH}{|}}{C}{=}NOH}$$

In fact, Lossen, generally attributed the "oximino" structure of the latter to the hydroxamic acids.

It is an interesting fact that although Lossen observed the rearrangement which bears his name, he never seems to have investigated this reaction in any detail.

An article by Yale [10] is still considered a useful review of the subject. Other useful reviews are those by Henecka and Kurtz [11], Metzger [12], Mathis [13], Smith [14], and Coutts [15a]. Reference [15b] is a more recent review with 114 references. A Russian book by Zhungistu and Artemenko is [15c].

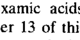
The physicochemical problems involved in the field are well summarized by Exner [2]. The topics discussed are the structure of hydroxamic acids, the chemistry of successive acylation of hydroxylamine, tautomerism, configuration, conformatiom, and the ionization of various acylated hydroxylamines. It is unfortunate that this article (in English) is in a somewhat inaccessible Danish pharmaceutical journal.

Exner's original papers, which cover many of these subjects, are generally to be found in the *Collection of Czechoslovakian Chemical Communications* such as in [15d]. An article by Exner in a British journal is [15e].

Reviews of those heterocyclic compounds that may be considered cyclic hydroxamic acids are to be found in Katritzky [16], Coutts [17], and Bapat et al. [18a].

Syntheses of heterocyclic systems have also been reviewed by Suwinski [18b].

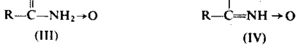
The chemistry of thiohydroxamic acids is reviewed in Walter and Schaumann [19a] and in Chapter 13 of this volume. The applications of O-acyl thiohydroxamates as sources of alkyl radicals in organic synthesis has been reviewed by D. Crich [19b]. In line with standard monographs on the chemistry of organic nitrogen compounds, such as Smith [14], and the work of Exner [2], regardless of the structures proposed by the authors cited in this chapter, we use the term "hydroxamic acid" for *N*-acyl derivatives of hydroxylamine (structure I).



$$R\text{—}\overset{\displaystyle O}{\overset{\|}{C}}\text{—}NHOH$$

(I)

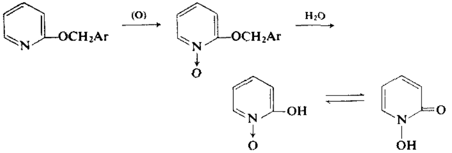
This structure may be in equilibrium with several other tautomeric forms (Eq. 1).



$$\begin{tikzcd} R\text{—}\overset{O}{\overset{\|}{C}}\text{—}NHOH \arrow[r, shift left] \arrow[d, shift left] & R\text{—}\overset{OH}{\overset{|}{C}}{=}NOH \arrow[l, shift left] \arrow[d, shift left] \\ R\text{—}\overset{O}{\overset{\|}{C}}\text{—}NH_2\rightarrow O \arrow[u, shift left] & R\text{—}\overset{OH}{\overset{|}{C}}{=}NH\rightarrow O \arrow[u, shift left] \end{tikzcd} \qquad (1)$$

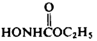
(I) (II) (III) (IV)

Structure (II) is most properly termed a "hydroximic acid." The free hydroximic acids apparently constitute only a minor component of the tautomeric equilibrium mixture although derivatives of hydroximic acids are known. Structures (III) and (IV) have been added to the list of possible tautomeric forms relatively recently [15a, 17]. Their importance becomes obvious from the standpoint of the preparation of cyclic hydroxamic acids. For example, the N-oxidation of an appropriately constituted molecule may produce a cyclic hydroxamic acid (Eq. 2) [20].

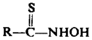


(2)

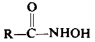
The primary focus of the present chapter is the preparation of hydroxamic acids of structure [I]. Related compounds are ethyl N-hydroxycarbamate cyclic hyroxamic acids and other N-substituted hydroxamic


$$\mathrm{HONH\overset{O}{\overset{\|}{C}}OC_2H_5}$$

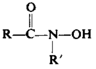
acids; *N,N*-diacylhydroxylamines as exemplified by *N*-hydroxyphthalimide; and thiohydroxamic acids:


$$\mathrm{R-\overset{S}{\overset{\|}{C}}-NHOH}$$

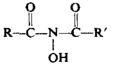
The variety of substituted hydroxamic acids is surprisingly large. If we consider only the structures which may be written upon alkylation and/or acylation of hydroxylamine but ignore the tautomeric derivatives, the following compounds result.


$$\mathrm{R-\overset{O}{\overset{\|}{C}}-NHOH}$$

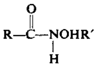
(I)


$$\mathrm{R-\overset{O}{\overset{\|}{C}}-\underset{R'}{\underset{|}{N}}-OH}$$

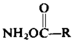
(V)


$$\mathrm{R-\overset{O}{\overset{\|}{C}}-\underset{OH}{\underset{|}{N}}-\overset{O}{\overset{\|}{C}}-R'}$$

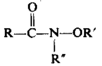
(VI)


$$\mathrm{R-\overset{O}{\overset{\|}{C}}-\underset{H}{\underset{|}{N}}OHR'}$$

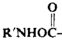
(VII)


$$\mathrm{NH_2O\overset{O}{\overset{\|}{C}}-R}$$

(VIII)

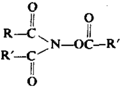

$$\mathrm{R-\overset{O}{\overset{\|}{C}}-\underset{R''}{\underset{|}{N}}-OR'}$$

(IX)

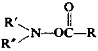


$R'NHOC(=O)-R''$

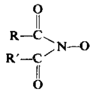
(X)



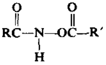
(XI)



(XII)

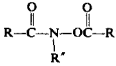


(XIII)



$RC(=O)-N(H)-OC(=O)-R'$

(XIV)



$R-C(=O)-N(R'')-OC(=O)-R'$

(XV)

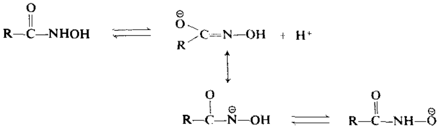
Compounds such as (VII), (IX), and (XIII) are esters of hydroxamic acids and in the case of structure (VII) are named alkyl hydroxamates.

When the distribution of electrons of hydroxamic acids and hydroximic acids are considered, it will be noted that several sites exist with which these compounds may act as nucleophilic reagents. While it is beyond the scope of this chapter to discuss the chemistry of these materials in great detail, from the preparative standpoint, it must still be kept in mind that the possibility of competitive reactions between the nitrogen atom and the "hydroxylamino" oxygen exists. Furthermore, that the hydroxamic acids may be acting as chelating agents must not be overlooked. Indeed, the classical color test for hydroxamic acids with ferric chloride involves chelation. Also, a common method of isolating these compounds by precipitation with cupric ions, while frequently referred to as a formation of "copper hydroxamate salts," is probably a case of the formation of copper chelates.

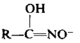
The acid strength of hydroxamic acids has been reported to be of the same order of magnitude as that of the carboxylic acids. At least some of these acids are said to be soluble in sodium bicarbonate solution. In actual fact, however, the acid strengths of hydroxamic acids vary over a wide range and some with $pK_a$ values of above 9 (e.g., *o*-methoxybenzohydroxamic acid) may be precipitated from an alkaline solution with carbon dioxide, provided, of course, that the free acid is insoluble in water [21].

The ionization of hydroxamic acid is somewhat complex. Not only are the free acids acidic, the esters as well as the *N*-alkyl derivatives are acidic, with $pK_a$ values of the same order of magnitude as those of free acids [2, 22]. The $pK_a$ value of hydroxamic acids are higher by three orders of magnitude than those of related hydroximic acids, indicating that these latter are weaker acids. On the other hand, *N,O*-diacylhydroxylamines are said to be even stronger acids than hydroxamic acids (that is, *N*-acylhydroxylamines) [2]. This leads to the assumption that the acidic properties of hydroxamic acids are associated with both the hydrogen of the "hydroxylamino" hydroxyl group and the hydrogen associated with the nitrogen atom itself.

The ionization of hydroxamic acids may be represented by Eq. (3) [22–25].

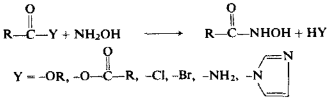

(3)

Another hydroxamate ion species

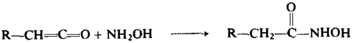

$$R{-}\overset{OH}{\overset{|}{C}}{=}NO^-$$

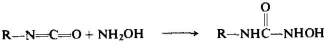
may also be in equilibrium with the forms indicated in Eq. 3, however, *if it* exists at all, its concentration is no more than $10^{-3}$ to $10^{-4}$ times the concentration of the other two species. These two hydroxamate ion exist in approximately equal concentrations [22].

The most important method for the preparation of hydroxamic acids is the acylation of hydroxylamine as shown in Eq. (4). Other acylation procedures of less importance are shown in Eqs. (5) and (6).


(4)

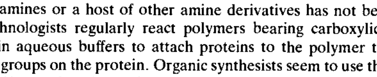
of less importance are shown in Eqs. (5) and (6).


$$R{-}CH{=}C{=}O + NH_2OH \longrightarrow R{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}NHOH \qquad (5)$$

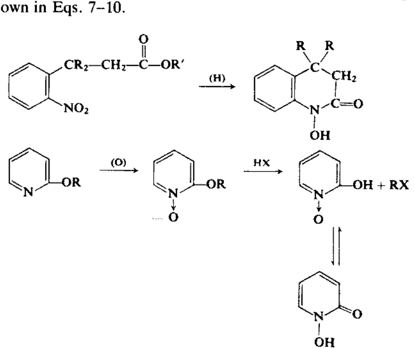

$$R{-}N{=}C{=}O + NH_2OH \longrightarrow R{-}NH\overset{O}{\overset{\|}{C}}{-}NHOH \qquad (6)$$

The acylation of either *N*- or *O*-substituted hydroxylamines by acid chlorides are also well known. There are examples of the formation of hydroxamic acids by reaction of carboxylic acids with hydroxylamine derivatives in the presence of a carbodiimide such as dicyclohexylcarbodiimide. The full potential of using carbodiimides, including such water-soluble ones as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride—usually called "EDC—for activating carboxylic acids for reactions with hydroxylamines or a host of other amine derivatives has not been realized. Biotechnologists regularly react polymers bearing carboxylic acids with EDC in aqueous buffers to attach proteins to the polymer through free amino groups on the protein. Organic synthesists seem to use this approach rarely, if at all. Yet the method is very elegant because it avoids the need to prepare and handle acid chlorides.

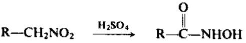
Methods of synthesis of hydroxylamic acids that are of less importance are shown in Eqs. 7–10.



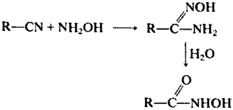
(7)



(8)



$$\mathrm{R{-}CH_2NO_2} \xrightarrow{\mathrm{H_2SO_4}} \mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}NHOH} \tag{9}$$

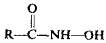


$$\mathrm{R{-}CN + NH_2OH} \longrightarrow \mathrm{R{-}C({=}NOH){-}NH_2} \xrightarrow{\mathrm{H_2O}} \mathrm{R{-}C({=}O){-}NHOH} \tag{10}$$

where R—CN is poly(acrylonitrile).

## A. Nomenclature

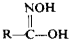
In the preceding discussion, we have already indicated that in this chapter we will use the term *hydroxamic acid* as represented by the structure



$$R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}NH{-}OH$$

(I)

The tautomeric isomer



$$R{-}\overset{\overset{\displaystyle NOH}{\|}}{C}{-}OH$$

will be referred to as a *hydroximic acid*. The geometric isomers of hydroximic acid derivatives (i.e., E- and Z-forms) are known in some cases.

In naming a specific compound, the practice is to drop the *ic* of the related carboxylic acid and substitute the letter *o* for it, followed by hydroxamic acid. Usually, if the letter *o* precedes *ic*, no second *o* is added. Thus, from benzoic acid we derive benzohydroxamic acid; from acetic acid, we obtain acetohydroxamic acid.

This system of nomenclature leads to some problems. For example, according to these rules, from caproic acid, we should derive caprohydroxamic acid; yet from capric acid, the hydroxamic acid would also be caprohydroxamic acid. Therefore, in these and similar cases, we have attempted to use the systematic names as the basis of nomenclature, i.e., hexanohydroxamic acid as the derivative of caproic acid, and decanohydroxamic acid as the derivative of capric acid.

Unfortunately, the journals do use such terms as "caprohydroxamic acid." The reader is therefore cautioned to examine the original literature very carefully to ascertain whether a derivative of caproic or of capric acid is meant.

In some cases, the original literature and even the abstracts have found it convenient to refer to some hydroxamic acids as *N*-acylhydroxylamine derivatives. This system may be particularly suitable when other *N*- and/or *O*-substituents are present.

In heterocyclic systems such as those derived from pyridine-2,6-dicarboxylic acid, we arbitrarily have decided to adapt the general rule for naming hydroxamic acids. Therefore, the dihydroxamic acid derived from this compound would be pyridine-2,6-dicarboxylohydroxamic acid—an admittedly awkward construction.

The cyclic hydroxamic acids usually derive their names from the heterocyclic systems to which they belong.

### B. Note on the Ferric Chloride Color Test

Throughout the literature on hydroxamic acids, reference is made to the use of ferric chloride solution as a color reagent for these compounds. Evidently hydroxamic acids with free hydroxylaminohydroxyl groups form complexes with ferric chloride variously described as red, wine-colored, burgundy, red-violet, violet, etc. We presume that the exact hue of the complex varies with structural features within the hydroxamic acid as well as the pH of the reagent, and the exact chemical composition of the complex. Suffice it to say the color of the complex may be presumed to fall in the range of violet to red of the artist's color wheel.

Generally the literature merely states that a sample is tested with a "ferric chloride solution." The exact composition is rarely given. Presumably for qualitative monitoring of the presence of hydroxamic acids, this composition is not critical. However, three suggested compositions are given here:

1. A 10% solution of $FeCl_3 \cdot 6H_2O$ in 0.7 *N* hydrochloric acid [26a–d].
2. A 2% solution of ferric chloride in 0.1 *N* hydrochloric acid [26a].
3. A solution containing 1.33% $FeCl_3$, 0.013 *M* HCl, and 0.5 *M* monochloroacetic acid. This solution is said to have the advantage of forming nonfading, stable complexes, which are insensitive to dilution [26d]. This reagent may be particularly valuable for colorimetric analyses.

Because hydroxamic acids are capable of chelation with many other metal ions, other color tests are conceivable, although not generally discussed in the literature.

## 2. CONDENSATION REACTIONS

**CAUTION:** Reports exist that severe explosions have taken place with reactions in which hydroxylamine or its common salts have been used. These observations were made upon scale-up of small laboratory preparations. Explosions with pure hydroxylamine hydrochloride and with hydroxylamine sulfate were noted on heating these reagents [27]. The factors involved in these explosions are not known, consequently no adequate precautions can be recommended. We suggest that hydroxylamine, its salts, or solutions containing any of these materials should never be exposed to temperatures above 60°C; the presence of peroxides or hydroperoxides (as in ether solutions) must be avoided; possibly all reactions should be carried out in inert atmosphere. All other precautions against explosive hazards should also be taken. In view of this hazard, all preparations involving hydroxylamine, its salts, or its derivatives, are given here for reference only and should not be construed as recommendations of safe reactions.

## A. Acylation of Hydroxylamine with Carboxylic Acids

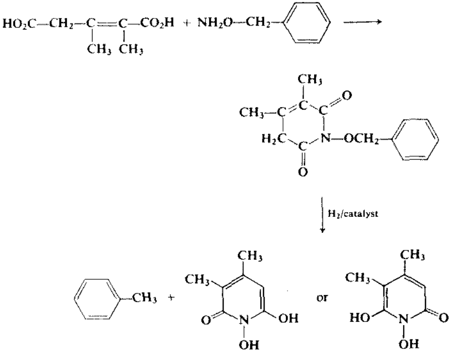
By analogy to the preparation of amides which involves the heating of an ammonium salt of a carboxylic acid, attempts have been made to dehydrate hydroxylammonium-carboxylates. In a few cases, at least a partial conversion to the hydroxamic acid seems to have taken place. However, in the few other cases reported, slightly above the melting point of the salt, the hydroxamic acids tended to decompose. Unfortunately this work was done with the haloacetic acids, which may have given rise to complex decompositions [28]. It is also conceivable that Lossen rearrangements may take place near the melting temperatures with consequent loss of insoluble hydroxamic acids. While attempts to use the dehydration of carboxylate salts of hydroxylamines may be worth investigating with the salts of the more stable carboxylic acids, the discussion in the remainder of this section will indicate a somewhat different direction which research should take, particularly in view of the potential explosion hazard on heating hydroxylamine salts.

During the early 1950s a controversy arose concerning the mechanism of hydroxamic acid formation in the presence of esterases in the liver and the pancreas. One group of researchers held that the enzymes hydrolyzed carboxylic esters to the free acid, which in turn reacted with hydroxylamine to form hydroxamic acids [29]. A second group [30] disputed this and demonstrated that enzymes could catalyze the reaction of esters with hydroxylamine to form hydroxamic acids.

Shortly thereafter, *O*-benzylhydroxylamine (benzyloxyamine) was reacted with $\alpha,\beta$-dimethylglutaconic acid under forcing conditions to produce *N*-benzyloxy-1,2-dimethylglutaconimide, which may be considered an ester of hydroxamic acid of the *N,N*-diacylhydroxylamine type [31]. On hydrogenation of this product, the corresponding hydroxamic acid [1,6(or 1,2)-dihydroxy-3,4-dimethylpyrid-2(or 6)-one (m.p. 157–158°C) could be isolated (Eqs. 11 and 12. This work showed that indeed free carboxylic acids could react with hydroxylamine derivatives to form hydroxamates.

Esters, however, may also serve to acylate hydroxylamine derivatives (e.g., Preparation 2-3).

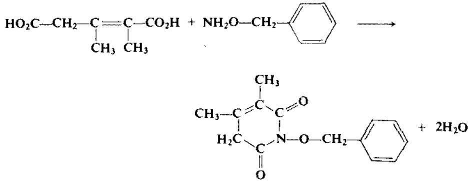
The first step of the foregoing preparation is given here as an early example of the formation of a hydroxamate ester. The hydrogenation is not discussed here because it is a standard technique of recovering a protected hydroxylamino group.



(11)

(12)

### *2-1. Preparation of* N-*Benzyloxy-1,2-dimethylglutaconimide* [31]



(13)

In an apparatus fitted with a reflux condenser and Dean–Stark trap, a dispersion of 1.0 gm (0.0063 mole) of $\alpha,\beta$-dimethylglutaconic acid, 0.8 gm (0.0065 mole) of *O*-benzylhydroxylamine (benzyloxamine), and 10 ml of xylene is heated under total reflux for 45 min until the water is separated. On cooling, 1.1 gm (71%) of the product precipitates; the melting point is 126–127°C (recrystallized from xylene).

In another study of the kinetics of hydroxylamine reactions with acylating agents, it has been stated that at elevated temperatures, hydroxylamine and unactivated acids will form hydroxamic acids in aqueous media in the pH range of 4–6. In dilute acid solutions, the acylation may proceed at 25°C. Since this paper was more of an attempt to resolve the controversy concerning the hydroxamic acid formation in biochemical systems, the synthetic possibilities were not explored [32].

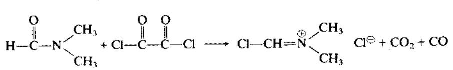
One patent indicates that phenoxyalkanolhydroxamic acid may indeed be prepared by the reaction of a free acid with hydroxylamine [33a]. Therefore, the possibility of using this simple method of preparing hydroxamic acids should be explored further. On reviewing the work of Jones and Werner [28] in the light of this idea, we find that salts of hydroxylamine and the simple acids seem to form on mixing the equivalent amounts of the reagents near 0°C. This products did not give the characteristic ferric chloride color test associated with hydroxamic acids. However, reaction conditions of pH and temperature may be found at which salt formation is suppressed and hydroxamic acid formation is enhanced. It must also be realized that if it is correct that *O*-ocylation of hydroxylamine takes place prior to rearrangement to the *N*-acyl derivative [26a], the reported salts might be *O*-acylhydroxylamines, possibly isolated as hydrates. *O*-Acylhydroxylamines do not give the ferric chloride color test. On the other hand, the salts under discussion were prepared under nonaqueous conditions so that the possibility of hydrate formation is reduced unless water had been introduced accidentally at some stage between the preparation and the analysis of the products.

A recent paper [33b] stated that the acylation of *N*-substituted hydroxylamines with mixed anhydrides, *N*-carboxyanhydrides of amino acids, active esters, or dicyclohexylcarbodiimide (DCC) may lead to both *N*- and *O*-acylation.

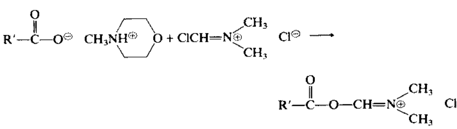
NOTE: The article in question is not clear as to how DCC was used. We presume that it was used with a carboxylic acid.
The authors found that tertiary amine salts of carboxylic acids and *N*-alkylhydroxylamines, in the presence of *N*,*N*-dimethylchloromethanimium chloride (from DMF and oxalylchloride), give *N*-alkylhydroxamic acids under mild conditions in one pot.

It should be noted that even their system, at times, led to *O*-acylation. Because the reaction is usually run in either methylene dichloride or chloroform, which are considered carcinogenic, and they also involve DMF and oxalyl chloride, two other hazardous chemicals, all due precautions must be taken. Carbon monoxide and carbon dioxide may also evolve, requiring further precautions.

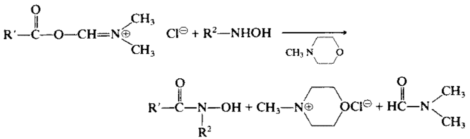
### 2-2. *Preparation of* N- *Alkylhydroxamic Acids, General Procedure Using* N,N-*Dimethylchloromethaniminium Chloride in One Pot* [33b]



(14)



(15)



(16)

With suitable safety precautions, in a reactor cooled to −20°C, to a mixture of 1 ml of dimethylformamide and 4 ml of methylene dichloride (or chloroform) is added dropwise a solution of 0.38 ml (4.4 mmol) of oxalyl chloride in methylene dichloride (or chloroform). After 20 min, 4 mmol of the carboxylic acid and 0.44 ml (4 mmol) of *N*-methylmorpholine are added. The mixture is stirred at −20°C for 20 min. Then 8 mmol of the *N*-alkylhydroxylamine and an additional 0.88 ml (8 mmol) of *N*-methylmorpholine is added. Stirring is continued for 4 hr after the reaction mixture has been allowed to cool to room temperature.

After diluting the reaction mixture with 10 ml of ethyl acetate, the mixture is washed in turn with 20 ml of 0.5 N hydrochloric acid, 30 ml of deionized water, and 20 ml of a 3% solution of sodium bicarbonate.

The product is isolated by extracting the *N*-alkylhydroxamic acid from the aforementioned mixture with aqueous 1-*N*-sodium hydroxide. The aqueous layer is separated and acidified by the cautious addition of concentrated sulfuric acid to a pH between 4 and 2.

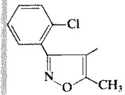
The mixture is cooled, and the product is extracted with two 20-ml portions of ethyl acetate. The combined extracts are washed with 30 ml of deionized water. The organic layer is then dried with anhydrous magnesium sulfate and filtered. The filtrate is evaporated to dryness. The crude hydroxamic acid is recrystallized (see Table I for solvents and properties of typical products.)

As indicated in Table I, the method appears to be of particular interest in preparing *N*-alkyl hydroxamic acids from amino acids and from their derivatives such as tosylates and benzyloxycarbonyl derivatives (not given in Table I but found in [33b].

Early work showing the use of DCC to prepare hydroxamic acids from carboxylic acids with hydroxamine are by Perez and coworkers [33,c]. The preparation method is quite simple. For example, a series of omega-halohydroxamic acids have been prepared in high yield and with few side reactions by simply treating the corresponding omega-halocarboxylic acid with hydroxylamine in methylene dichloride and adding DCC, filtering off the solid dicyclohexyl urea coproduct, and isolating the hydroxamic acid by

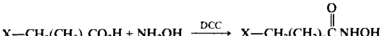
TABLE I

*N*-ALKYL-HYDROXAMIC ACIDS $(R_1—\overset{O}{\overset{\|}{C}}—N(R_2)OH)$ PREPARED BY *N,N*-DIMETHYLCHLOROMETHANIMINIUM CHLORIDE METHOD [33b]

| $R_1$ | $R_2$ | Yield (%) | M.p. (°C) (solvent) | IR (KBr) $\nu(cm^{-1})$ of —CO--N(OH)— |
|---|---|---|---|---|
| $C_6H_5—$ | CH—$CH_3$<br>$C_6H_5$<br>(oil) | 54<br>(37)[a] | 116<br>(ethanol/water) | 1610 |
| $C_6H_5$ | $C_2H_5$ | 66 | 66<br>(ether/hexane) | 1640 |
| Z-L-Ala | $C_2H_5$ | 64 | 90–92<br>($CHCl_3$/Hexane) | 1645 |
| Tos-L-Leu | $C_2H_5$ | 68 | 162–164<br>(ethyl acetate/hexane) | 1610 |
| Z-Gly- | $C_6H_4$ | 48<br>(36)[a] | 132–133<br>($CHCl_3$/hexane) | 1640 |
| $C_6H_5$—CH CH— | $C_2H_5$ | 70 | 95–97<br>($CHCl_3$/hexane) | 1645 |
|  | $C_2H_5$ | 70 | 146–148<br>(ethyl acetate/hexane) | 1645 |

[a] Yield (%) of *O*-acyl derivative, as analyzed by $^1H$–NMR

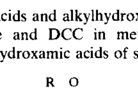
evaporating the solvent and recrystallizing. The reaction may be represented by Eq. 17 [33c].



$$X{-}CH_2(CH_2)_nCO_2H + NH_2OH \xrightarrow[CH_2Cl_2]{DCC} X{-}CH_2(CH_2)_n\overset{O}{\overset{\|}{C}}NHOH \quad (17)$$

Table II shows the omega-halohydroxamic acids prepared by Bittner [33e].

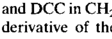
Treating thienylglycolic acids and alkylhydroxylamine hydrochloride in ethanol with triethylamine and DCC in methylene dichloride forms thienyl-substituted glycolohydroxamic acids of structure [XVI),



(XVI)

where R may be H, $CH_3$, $CH(CH_3)_2$, cyclohexyl, benzyl, $C_6H_5$ and R′ may be H, $CH_3$, $C_2H_5$, or benzyl [33f].

We recently had occasion in one of our laboratories (W.K.) to attempt Bittner's reaction using equimolar amounts of an amino acid, acrylic acid, and DCC in $CH_2Cl_2$. A reaction took place rapidly, to form the acrylamide derivative of the amino acid and a white precipitate. From the melting point of the coproduct, we identified it as mono-cyclohexylurea rather than the expected dicyclohexylurea. We mention this experience here to illustrate the simplicity of this general method of preparing a wide range of



$R{-}\overset{O}{\overset{\|}{C}}{-}NR_2{-}$type products.

Polymers containing acrylic acid units in their backbone are readily reacted to amino groups on proteins such as collagen, in an aqueous buffer,

TABLE II

ω-HYDROXAMIC ACIDS PREPARED BY THE CARBODIIMIDE METHOD (EQ. 17) [33e]

| Hydroxamic Acid | M.p. (°C) | Yield (%) | Crystallization solvent |
|---|---|---|---|
| Chloroaceto | 108 | 79 | Acetone-petroleum ether |
| β-Chloropropiono | 104–105 | 72 | Methyl ethyl ketone |
| γ-Chlorobutyro | oil | 78 | — |
| δ-Chlorovalero | oil | 82 | — |
| ω-Bromoundecano | oil | 74 | — |

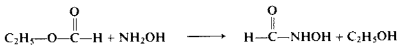
by use of the water-soluble carbodiimide 1-cyclohexyl-3-[2-morpholinyl-(4)-ethyl] carbodiimide metho-*p*-toluene sulfonate (sometimes called WSC) [33g,h].

We have no doubt that polymeric hydroxamic acids can be prepared easily by treating a copolymer containing carboxylic acid moieties with hydroxylamine in the presence of a carbodiimide such as WSC. Again, we (W.K.) frequently react copolymers of styrene and methacrylic acid with EDC (i.e., 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) in aqueous buffer and react the product with poteins such as monoclonal antibodies to bind the protein to the polymer. This reaction is very facile and should be easily extended to forming hydroxamic acid units on the surface of a suitable polymer. (We would be glad to furnish a typical protocol to interested readers, upon written request.)

## B. Acylation of Hydroxylamine with Esters

The reaction of ammonia or amines with esters to prepare amides frequently gives indifferent results, and alternate routes are used. On the other hand, the analogous reaction of hydroxylamine or substituted hydroxylamines with esters is the most widely used synthesis of hydroxamic acids. While the results are sometimes not satisfactory, the ready availability of the esters and the simplicity of the reaction encourage using this method in all initial attempts to prepare hydroxamic acids [10–62]. Several examples illustrating this method are shown in Table III and Preparations 2-3 to 2-6.

### *2-3. Preparation of Formohydroxamic Acid* [36]



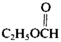
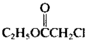
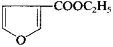
$$C_2H_5{-}O{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}H + NH_2OH \longrightarrow H{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}NHOH + C_2H_5OH \qquad (18)$$

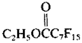
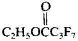
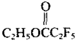
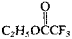
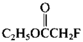
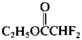
(*a*) *Preparation of hydroxylamine solution.* Thirty grams (0.43 mole) of hydroxylamine hydrochloride is dissolved in 150 ml of boiling methanol. The solution is cooled somewhat and a solution of 9.9 gm (0.43 gm-atom) of sodium in 150 ml of methanol is added cautiously. The mixture is cooled and then placed in an ice-salt bath until the sodium chloride formed has been precipitated as completely as possible. After the sodium chloride has been filtered off, approximately 200 ml of the methanol is distilled off under reduced pressure. The still residue is again filtered and then used directly in the next step.

## TABLE III

PREPARATION OF HYDROXAMIC ACIDS BY THE ACYLATION OF HYDROXYLAMINE ESTERS

$RCOOR'—NH_2OH—RCONHOH—R'OH$

| Acylating agent (moles) | Hydroxylamine[a] (moles) | Solvent (ml) | Reaction conditions | | Yield of RCONHOH (%) | M.p. (°C) | Ref. |
|---|---|---|---|---|---|---|---|
| | | | Temp. (°C) | Time (hr) | | | |
|  $C_2H_5O\overset{O}{\overset{\|}{C}}H$<br>(0.37) | 0.5[b] | $H_2O$<br>(100) | 0–25 | 4 | 35 | 77.5 | 26d |
| (0.42) | 0.43 | $CH_3OH$<br>(150) | 0–25 | 3–4 | 70 | 81–82 | 36 |
|  $C_2H_5O\overset{O}{\overset{\|}{C}}CH_2Cl$<br>(0.082) | 0.061 | $H_2O$<br>(10) | 0–10 | 3 | 80 | 92–93 | 28, 37 |
| (0.527) | 0.527 | $C_2H_5OH$<br>(10) | − 10 to − 8 | 2 | 58 | 86–87 | 38 |
| <br>(0.238) | 0.29 | $CH_3OH$<br>(150) | 25 | 10 | 80 | 119–122 | 39 |
| $(CH_3)_3N—C_6H_4—COOCH_3I^{\ominus}$<br>(0.093) | 0.22 | $CH_3OH$<br>(100) | 25 | 45 | 36 | 193.5–195 | 50 |
| $C_6H_5COOC_2H_5$<br>(0.1) | 0.20 | Pyridine<br>(120) | 0–5 | 6 | 91 | 131 | 52 |
| $(CH_2)_n(COOR)_2$<br>(0.5) | 1.00 | $C_2H_5OH$<br>(1000) | 0–5 | 5–6 | 90<br>(1/2 ester) | — | 49, 55–57 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| $C_2H_5COO(CH_2)_8CONH_2$<br>(0.022) | 0.024 | $C_2H_5OH$<br>(10) | 0–25 | 1–1½ | 61 | 120–123.5 | 49 |
|  $C_2H_5O\overset{\overset{O}{\|}}{C}C_7F_{15}$<br>(0.45) | 0.45 | $CH_3OH$<br>(300) | 25 | 16 | 87 | 115–116<br>from<br>(acetonitrile) | 62d |
|  $C_2H_5O\overset{\overset{O}{\|}}{C}C_3F_7$<br>(0.45) | 0.45 | $CH_3OH$ | 25 | 16 | — | 89–92<br>(benzene) | 62d |
|  $C_2H_5O\overset{\overset{O}{\|}}{C}C_2F_5$<br>(0.45) | 0.45 | $CH_3OH$ | 25 | 16 | — | 65–67<br>(benzene) | 62d |
|  $C_2H_5O\overset{\overset{O}{\|}}{C}CF_3$<br>(0.45) | 0.45 | $CH_3OH$ | 25 | 16 | — | 49–51<br>($CH_2Cl_2$) | 62d |
|  $C_2H_5O\overset{\overset{O}{\|}}{C}CH_2F$ | 0.45 | $CH_3OH$ | 25 | 16 | 82 | 92–94 | 62e |
|  $C_2H_5O\overset{\overset{O}{\|}}{C}CHF_2$ | 0.45 | $CH_3OH$ | 25 | 16 | 94 | oil<br>$n_D^{25}$ 1.4402 | 62e |

[a] From hydroxylamine hydrochloride plus base. [b] From hydroxylamine sulfate plus base.

(*b*) *Preparation of formohydroxamic acid.* The hydroxylamine solution, prepared as above, is cooled at 0°C. Then 31 gm (0.42 mole) of ethyl formate is added. During this addition an increase in temperature is observed. This is moderated by cooling in a stream of running water. After the addition has been completed, the reaction mixture is allowed to stand at room temperature for several hours.

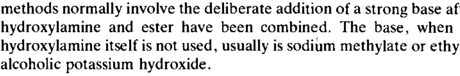
The excess methanol is evaporated from the reaction mixture under reduced pressure. The crystalline residue is contaminated with a small amount of an oily substance and some sodium chloride. The oily material is removed by pressing the crude product on an unglazed clay plate. The yield is 17.9 gm (70%). The product is crystallized from ethyl acetate. During this process, the remaining sodium chloride is separated by filtration of the hot solution. The final product melts at 81–82°C.

**CAUTION:** The product is said to explode above its melting point.

While some hydroxamic acids have been prepared without significant excesses of either hydroxylamine or of a stronger base, the preferred methods normally involve the deliberate addition of a strong base after the hydroxylamine and ester have been combined. The base, when excess hydroxylamine itself is not used, usually is sodium methylate or ethylate or alcoholic potassium hydroxide.

The preparation of 3-furohydroxamic acid (pyromucohydroxamic acid or "pyromucylhydroxamic acid") is an example of the technique.

### *2-4. Preparation of 3-Furohydroxamic Acid* [39]



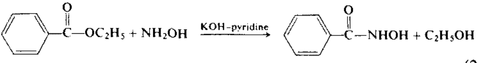
(19)

To a solution of a total of 150 ml of methanol to which has been added 19.5 gm (0.29 mole) of hydroxylamine hydrochloride and a solution of 6.4 gm (0.28 gm-atom) of sodium in methanol, is added 30 gm (0.238 mole) of ethyl furoate. Then a solution of 5.4 gm (0.23 gm-atom) of sodium in 70 ml of methanol is added to the mixture, which is thereupon stored for 10 hr.

With due safety precautions, the reaction is cautiously made acidic with concentrated hydrochloric acid. The sodium chloride with precipitates is separated by filtration. The filtrate is concentrated by distillation under reduced pressure. The residual oil, stored under reduced pressure in a vacuum desiccator, solidifies after a few hours. After recrystallization from water, the product has a melting range of 119–122°C. The yield is 24 gm

(80%). The recrystallizing solvent retains a small amount of product. This may be demonstrated by adding cupric acetate to the solvent, whereupon the copper chelate of the hydroxamic acid precipitates (approx. 3 gm).

### *2-5. Preparation of Benzohydroxamic Acid in Pyridine* [52]



(20)

To a rapidly stirred suspension of 19.6 gm (0.35 mole) of powdered anhydrous potassium hydroxide in 120 ml of pyridine, maintained at 0–5°C, is a added a solution of 13.9 gm (0.2 mole) of hydroxylamine hydrochloride in 100 ml of pyridine.

While maintaining the reaction temperature at 0–5°C, 15 gm (0.1 mole) of ethyl benzoate is added. Vigorous stirring is continued at room temperature for 6 hr. Then the solids are filtered off. The solids are washed with cold water to remove inorganic coproducts. The remainder, recrystallized from aqueous ethanol, represents a 94% yield of potassium benzohydroxamate.

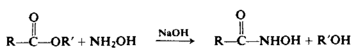
This salt is triturated with cold 0.01 *N* hydrochloric acid. From this mixture, by the usual procedures, 12.5 gm (91% overall) of benzohydroxamic acid is isolated, m.p. 131°C (from aqueous alcohol).

By a similar procedure, a quantitative yield of laurohydroxamic acid (not described further) is said to have been prepared from methyl laurate. *p*-Nitrobenzohydroxamic acid was prepared in only a 17% yield by this method.

The general procedure of reacting aliphatic esters with hydroxylamine as described so far has been criticized because it does not lend itself well to the preparation of large quantities (100-gm scale). By careful attention to details such as the order of addition, adding the ester to a strongly alkaline hydroxylamine solution at such a rate that the ester dissolves completely in the reaction medium (with additional ethanol if necessary), the reaction is said to be completed within a few minutes at least to the extent of 90% [26b]. Generalized directions for this procedure are given here. This procedure may be scaled up to at least 1 *M* level by multiplying all quantities by a constant factor. By this method, formo-, aceto-, propio-, and isobutyrohydroxamic acids have been prepared. It was not completely satisfactory for the preparation of *n*-butyro-, valero-, and γ-hydroxybutyrohydroxamic acids.

It should be recalled, however, that there is an explosive hazard associated with the scale-up of these preparations.

### *2-6. Generalized Preparation of Aliphatic Hydroxamic Acids* [26b]



$$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}OR' + NH_2OH \xrightarrow{NaOH} R{-}\overset{O}{\overset{\|}{C}}{-}NHOH + R'OH} \qquad (21)$$

$R' = C_2H_5$ or $CH_3$
(Scale: 0.1 *M*)

In a well-ventilated hood, with a magnetic stirrer running in a 250 ml, round-bottomed flask, to a solution of 15 ml of distilled water and 12 ml of absolute ethanol is added, in small portions to assure complete dissolution 7 gm (0.1 mole) of dry hydroxylamine hydrochloride.

When solution is complete, a tray of an ice-water mixture is inserted between the flask and the magnetic stirrer motor to cool the flask contents. While maintaining an internal temperature below 20°C, 20 ml of 10 *N* aqueous sodium hydroxide (0.2 mole) is added slowly. The ice is removed when the addition has been completed and, with continued stirring, 0.1 mole of the ethyl or methyl ester of the desired carboxylic acid is added dropwise at such a rate that the ester completely solubilizes before another portion is added. If necessary small quantities of ethanol are added to assure complete solubilization. After this addition has been completed, stirring is continued for 1–2 hr.

The flask contents are then again cooled by inserting an ice tray under the flask. Provisions are made to remove vapors from the flask by directing a gentle compressed air stream on the inner lip of the flask and, with continued stirring, 7.5 ml (0.09 mole) of conc. hydrochloric acid is slowly added until the end point, as detected with pH paper, of pH-6 is reached. Usually, just prior to reaching this end point the flask contents become cloudy because of the precipitation of sodium chloride.

The flask is then attached to a rotary evaporator and the reaction mixture is evaporated to a slurry of crystals in a viscous yellow oil at 1–10 mm Hg using a water bath at 50°C to warm the flask (usually requires several hours). To this slurry, 100 ml of absolute ethanol is added and evaporation is resumed. When no more fluid remains, this step is stopped. The crystals are scraped off and extracted two times with 100-ml portions of boiling, ethyl acetate as follows:

The requisite quantity of boiling ethyl acetate is added to the flask and stirred vigorously. After a few minutes, when boiling has just stopped, the sodium chloride is allowed to settle and the extract is decanted into an Erlenmeyer flask. This step is then repeated. The separation of the product solution from sodium chloride usually does not require filtration.

To the warm ethyl acetate solution, spectral grade acetone is added dropwise to convert unreacted hydroxylamine to acetoxime which is quite soluble in cold ethyl acetate. (The amount of acetone required may be measured by estimating the hydroxylamine level with acidified Nessler reagent [26c].)

The solution is then concentrated by boiling until a faint cloudiness appears. Then the solution is gradually cooled to room temperature, followed by overnight storage in a freezer (at −15°C). The product is collected and washed in turn with cold ethyl acetate and with cold ether. Finally, the product is stored under reduced pressure for approximately 1 week in a vacuum desiccator over phosphorus pentoxide or conc. Sulfuric acid. Yields: formohydroxamic acid, 30%; acetohydroxamic acid, 60%; propiohydroxamic acid, 50%; isobutyrohydroxamic acid, 60%.

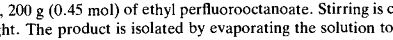
Methyl esters of medium molecular weight carboxylic acids (up to about $C_9$) are said to react even on an industrial scale with a small molar excess of hydroxylamine sulfate in water solution [62b]. The additions of surfactants and aqueous sodium hydroxide have also been suggested [62c].

The major, characteristic infrared absorption bands for these hydroxamic acids are 3,2 $\mu$ (N—H vibration) and 6.2 $\mu$ (C—O vibration). Paper or thin-layer chromatography of these products has been carried out using either butanol saturated with water, butanol saturated with 10% aqueous ammonia, or *t*-pentanol saturated with 10% aqueous ammonia. The chromatographs were developed with 2% ferric chloride in 0.1 *N* hydrochloric acid compounded with 95% ethanol for spraying.

Perfluoroalkanohydroxamic acids have also been prepared by acylation of hydroxylamine with the corresponding ethyl ester (Preparation 2-7) [62d,e]

### *2-7. Preparation of Perfluorooctanohydroxamic Acid* [62d]

$$NH_2OH \cdot HCl + NaOCH_3 \longrightarrow NH_2OH + NaCl + CH_3OH \tag{22}$$



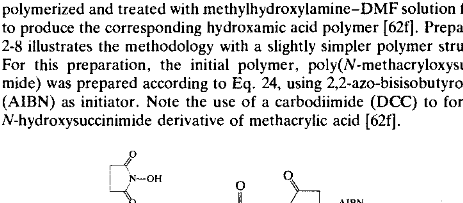
$$CF_3(CF_2)_6\overset{O}{\overset{\|}{C}}OC_2H_5 + NH_2OH \longrightarrow CF_3(CF_2)_6\overset{O}{\overset{\|}{C}}NHOH + C_2H_5OH \tag{23}$$

With suitable safety precautions, to 300 ml of methanol (in which 24.45 g (0.45 mol) of sodium methoxide has been dissolved) is added, portionwise, 31.45 g (0.45 mol) of hydroxylamine hydrochloride. The precipitating sodium chloride is filtered off.

To the methanolic solution of hydroxylamine is added dropwise, with stirring, 200 g (0.45 mol) of ethyl perfluorooctanoate. Stirring is continued overnight. The product is isolated by evaporating the solution to dryness. Yield: 168.28 g (87%). The product may be recrystallized from acetonitrile: m.p. 115–116°C; IR (KBr) 1690 cm$^{-1}$ (CO).

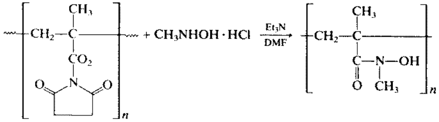
Other fluorinated hydroxamic acids prepared by similar procedures are given in Table III.

Polymeric methacrylic ester derivatives have been converted to polymeric hydroxamic acids by reaction with hydroxylamine derivatives. For example, the *N*-hydroxysuccinimide ester of *N*-methacryloyl $\beta$-alanine was polymerized and treated with methylhydroxylamine–DMF solution for 7 h to produce the corresponding hydroxamic acid polymer [62f]. Preparation 2-8 illustrates the methodology with a slightly simpler polymer structure. For this preparation, the initial polymer, poly(*N*-methacryloxysuccinimide) was prepared according to Eq. 24, using 2,2-azo-bisisobutyronitrile (AIBN) as initiator. Note the use of a carbodiimide (DCC) to form the *N*-hydroxysuccinimide derivative of methacrylic acid [62f].



(24)

### *2-8. Preparation of Poly (N-Methylmethacrylohydroxamic Acid)* [62f]



(25)

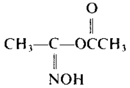
A solution of 0.68 g (8.2 millimol) of *N*-methylhydroxylamine hydrochloride in dry DMF is treated with a solution of 0.83 g (8.2 mmol) of anhydrous triethylamine in DMF. After removal of the precipitated salt by filtration, the filtrate is added to a solution of 0.50 g (2.7 m equiv. of monomeric residue) of poly(*n*-methacryloxysuccinimide) in 10 ml of dry DMF. The mixture is stirred for 2 hr and then passed through a 2.5 × 70 cm column packaged with Sephadex G-25 to desalt the solution. Additional DMF is added to the column to collect a total of 108 ml of effluent. The effluent is evaporated to dryness to yield 0.304 g of the polymeric hydroxamic acid (97% yield).

## C. Acylation of Hydroxylamines with Acid Anhydrides and Acyl Halides

The acid anhydrides and acyl halides have been used to prepare hydroxamic acids. Because of the reactivity of these reagents, frequently there is a loss of desired product because diacylation may take place to produce *N,N*-diacyl-hydroxylamines.

An early paper implies that whereas the reaction of aromatic acid chlorides with hydroxylamine may proceed in a straightforward fashion, aliphatic acid chlorides are decomposed by hydroxylamine. Subsequent workers were more successful with acid chlorides and were able also to use acid anhydrides in place of the acid chlorides [63–81b].

As was mentioned in connection with the acylation of hydroxylamine with esters, there is some evidence that acyl halides and anhydrides initially acylate the hydroxyl oxygen. This reaction is followed by a more or less rapid rearrangement from the *O*-acylhydroxylamine to the hydroxamic acid [26a]. In the case of acylation with anhydrides, it has also been proposed that "diacetylhydroxamic acid"

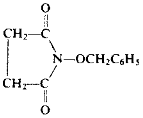
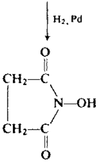


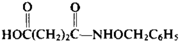
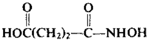
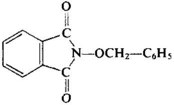
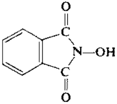
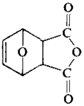
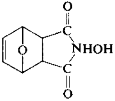
$$\mathrm{CH_3{-}\underset{\underset{NOH}{\|}}{C}{-}O\overset{\overset{O}{\|}}{C}CH_3}$$

forms initially [63]. As evidence is cited the observation that upon treatment with cupric acetate, the reaction mixture does not cause the precipitation of the cupric-hydroxamic acid complex. Only after the reaction mixture has been neutralized can the presence of a hydroxamic acid be demonstrated. Since the reaction is carried out with 2 moles of anhydride permole of hydroxylamine, these observations are not entirely surprising. Several examples of the preparation of hydroxamic acids by the acylation of hydroxylamine and derivatives are given in Table IV and Preparations 2-9 to 2-12.

# TABLE IV

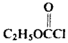
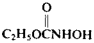
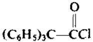
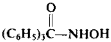
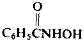
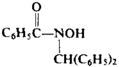
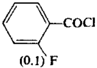
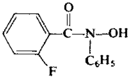
## Preparation of Hydroxamic Acids by Acylation of Hydroxylamine and Derivatives

| Acylating agent (moles) | Hydroxylamine or derivative (moles) | Solvent (ml) | Reaction conditions | | Product | Yield (%) | M.p. (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|
| | | | Temp. (°C) | Time (hr) | | | | |
| Succinic anhydride<br>(0.008) | $C_6H_5CH_2ONH_2$<br>(0.008) | $C_6H_6$ | 180 | 1/2 |  | 76 | 140–141 | 31 |
| | | | | |  | — | 92–98 | |
| (0.291) | $NH_2OH$<br>(0.291) | Toluene<br>1200 | 110 | 4 | Same as above | 49 | 92–98 | 69 |

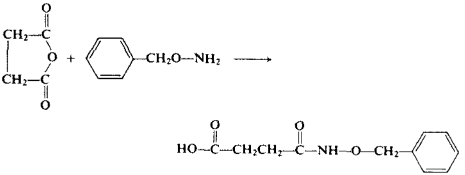
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| (0.05) | $C_6H_5CH_2ONH_2$<br>(0.05) | Toluene<br>(120) | 80 | 1 |  $HO\overset{O}{C}(CH_2)_2\overset{O}{C}—NHOCH_2C_6H_5$ | 68 | 95–96 | |
| | | | | | $\downarrow$ $H_2$, Pd<br> $HO\overset{O}{C}(CH_2)_2—\overset{O}{C}—NHOH$ | 56 | 95–96 | |
| Phthalic Anhydride<br>(0.135) | $C_6H_5CH_2ONH_2$<br>(0.138) | Xylene<br>(500) | 135–140 | 1 |  | 90 | — | 68 |
| | | | | | $\downarrow$ $H_2$, Pd<br> | 74 | 232–233 | |
| <br>(0.06) | $NH_2OH$<br>(0.06) | $CH_3OH$<br>(50)<br>$CH_3ONa$<br>(0.06 mole) | 56 | 1 |  | 80 | 165–166 | 21 |

(*continues*)

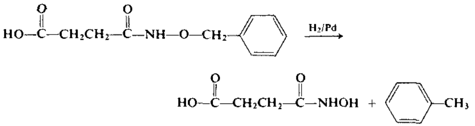
TABLE IV (*Continued*)

| Acylating agent (moles | Hydroxylamine or derivative (moles) | Solvent (ml) | Reaction conditions Temp. (°C) | Reaction conditions Time (hr) | Product | Yield (%) | M.p. (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|
|  $C_2H_5OC(=O)Cl$<br>(0.276) | $NH_2OH$<br>(0.281) | — | — | — |  $C_2H_5OC(=O)NHOH$ | 76 | — | 36 |
|  $(C_6H_5)_3C—C(=O)Cl$<br>(0.0082) | $NH_2OH$<br>(0.0756) | $C_6H_6$<br>(40) | 25 | 1–2 |  $(C_6H_5)_3C—C(=O)—NHOH$ | 81 | 175–176 | 39 |
| $C_6H_5COCl$<br>(0.02) | $NH_2OH$<br>(0.02) | Ether<br>(50) | 25 | 1/2 |  $C_6H_5C(=O)NHOH$ | 95–100 | 124–125 | 39 |
| $C_6H_5COCl$<br>(0.05) | $(C_6H_5)_2CHNHOH$<br>(0.025) | $H_2O$<br>(50) | 25 | 1 |  $C_6H_5C(=O)—N(OH)CH(C_6H_5)_2$ | 58 | 192 | 76 |
|  (0.1) | $C_6H_5NHOH$<br>(0.1) | Ether<br>(150) | 0 | 1–2 |  | 80 | 129 | 81a |

### 2-9. *Preparation of Succinomonohydroxamic Acid (N-Hydroxysuccinamic Acid) via N-Benzyloxysuccinamic Acid* [31]



(26)

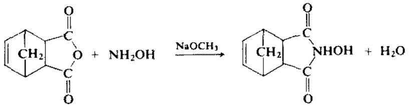


(27)

To a refluxing solution of 5.0 gm (0.05 mole) of succinic anhydride in 100 ml of benzene is added a solution of 6.3 gm (0.05 mole) of *O*-benzylhydroxylamine in 20 ml of benzene. As soon as the addition has been completed, the reaction mixture is cooled, and the precipitated product is separated. Upon recrystallization from a benzene-methyl ethyl ketone mixture, 7.6 gm (68.2%) of *N*-benzyloxysuccinamic acid, m.p. 95–96°C isolated.

A suspension of 4.3 gm (0.0193 mole) of this intermediate and a strontium carbonate catalyst containing 5% palladium in methyl ethyl ketone is hydrogenated. Upon working up the reaction mixture, 1.45 gm (56.7%) of succinomonohydroxamic acid, m.p. 95–96°C is isolated.

### 2-10. *Preparation of N-Hydroxy-3,6-endo-methylene-$\Delta^4$-tetrahydrophthalimide* [21]



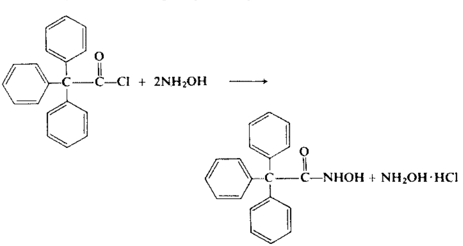
(28)

To a solution of 9.85 gm (0.06 mole) of *endo-cis*-3,6-*endo*-methylene-$\Delta^4$-tetrahydrophthalic anhydride in 50 ml of methanol is added with stirring a methanol solution containing 1.98 gm (0.06 mole) of hydroxylamine and 2.4 gm (0.06 mole) of sodium methylate. The reaction mixture is kept at room temperature for 24 hr, after which a small quantity of a precipitate is observed in the reaction flask. The solvent is removed by evaporation under reduced pressure. The residue is dissolved in a minimal quantity of water. Upon acidification, the product precipitates. The product is filtered off and recrystallized from chloroform-ligroin (b.p. range 60–90°C) mixture. The yield is 8.6 gm (80%), m.p. 165–166°C.

In ethanol solution, succinic anhydride and maleic anhydride reacted with hydroxylamine to produce the monohydroxamic acids, i.e., *N*-hydroxysuccinamic acid and *N*-hydroxymaleamic acid, respectively, in somewhat impure from [49].

Another method of preparing *N*-hydroxysuccinimide has been proposed. In this procedure, the reaction is carried out in an inert solvent, which permits forcing conditions for the final cyclization [64].

### *2-11. Preparation of Triphenylacetohydroxamic Acid* [39]



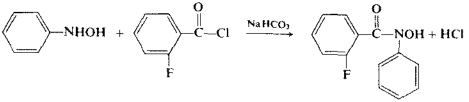
(29)

To a flask containing 2.5 gm (0.0756 mole) of hydroxylamine is added a solution of 2.5 gm (0.0082 mole) of triphenylacetyl chloride in 40 ml of anhydrous benzene with frequent shaking during the first hour after completion of the addition. The reaction mixture is stored overnight at room temperature.

The benzene layer is separated from the excess hydroxylamine by decantation into a distillation flask. The solvent is removed by distillation. On cooling, the oily residue crystallizes; addition of petroleum ether causes additional precipitation. The crude yield is 2 gm (81%), m.p. 172°C. Upon recrystallization from peroxide-free ether, the melting range is raised to 175–176°C.

By a similar procedure, diphenyl-*p*-tolylacetohydroxamic acid was prepared using petroleum ether as the solvent (m.p. 146.5°C) [70].

### *2-12 Preparation of N-Phenyl-o-fluorobenzohydroxamic Acid [81a]*

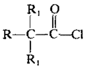


(30)

To a dispersion of 10.9 gm (0.1 mole) of freshly recrystallized *N*-phenylhydroxylamine, a solution of 12.0 gm (0.15 mole) of sodium bicarbonate in 25 ml of water, and 150 ml of peroxide-free ether, cooled to 0°C and vigorously stirred is added dropwise over a 1-hr period a solution of 23.12 gm (0.1 mole) of *o*-fluorobenzoyl chloride in 100 ml of peroxide-free ether. After the addition has been completed, stirring at 0°C or below is continued for 0.5 hr. If some of the product precipitates, it is separated by filtration and reserved. The ethereal solution is evaporated under reduced pressure. The residue is combined with the precipitate and triturated in a porcelain mortar for 15 min with a saturated solution of sodium bicarbonate in water to remove acidic impurities. The solids are filtered off, washed with cold water, and air-dried. The crude yield is 18.5 gm, m.p. 125°C. After two recrystallizations from benzene-petroleum ether the melting point was raised to 129°C.

Other *N*-arylhydroxamic acids have been prepared by this method [81b]. To prevent the product from oiling out, it has been suggested that the reaction be run in a petroleum ether (b.p. 40–60°C) diethyl-ether solvent system under a carbon dioxide blanket [81c]. Table V lists a few *N*-arylhydroxamic acids prepared by this modified procedure. Table VI lists primarily ring-substituted aromatic hydroxamic acids prepared by the acylation of the appropriate hydroxylamine derivatives with acid chlorides or esters.

Acid chlorides with considerable branching (i.e., of structure



$$R-\underset{R_1}{\overset{R_1}{C}}-\overset{O}{\overset{\|}{C}}-Cl$$

where R may be alkyl chains from $C_4$ to $C_{10}$ and $R_1$ may be $C_1$ to $C_4$, phenyl, or cyclohexyl groups) react with hydroxylamine to form trialkylacetohydroxamic acids, which are said to be stabilized by the tertiary alkyl groups [81j].

### TABLE V

*N*-ARYLHYDROXAMIC ACIDS [81c]

| Hydroxamic Acid | M.p. (°C) | Yield (%) |
|---|---|---|
| *N*-(*p*-chlorophenyl)-*o*-bromobenzo | 151 | 89 |
| *N*-(*p*-chlorophenyl)-*p*-bromobenzo | 162 | 76 |
| *N*-(*p*-chlorophenyl)-*o*-nitrobenzo | 165 | 67 |
| *N*-(*n*-tolyl)-1-naphtho | 126 | 53 |
| *N*-(*p*-chlorophenyl)-1-naphtho | 171 | 82 |
| *N*-(*m*-tolyl)-2-theno | 80 | 76 |
| *N*-(*p*-chlorophenyl)-2-theno | 143 | 80 |
| *N*-(*p*-chlorophenyl)-*p*-chlorophenoxyaceto | 113 | 50 |

### TABLE VI

MISCELLANEOUS HYDROXAMINE ACIDS

| Hydroxamic acid | M.p.(°C) | Crystalizing solvent | Ref. |
|---|---|---|---|
| *o*-Chlorobenzo | 159.5–160.1 | Toluene | [81*d*] |
| *o*-Methylbenzo | 130.5–131 | Ethyl Acetate | [81*d*] |
| *o*-Bromobenzo | 177.5–178.5 | Ethanol/Water 3:7 | [43, 81*d*] |
| *o*-Methoxybenzo | 124–126 | Ethanol/Water 3:7 | [43, 81*d*] |
| *o*-Ethoxybenzo | 124–125 | Ethanol/Water 3:7 | [43, 81*d*] |
| *N*-Methyl-2-methylbenzo | 120–121 | Benzene, $CCl_4$ | [81*e*] |
| *N*-Methyl-2-chlorobenzo | 118–119 | Benzene, $CCl_4$ | [81*e*] |
| *N*-Methyl-4-methylbenzo | 119–120 | — | [81*e*] |
| *N*-Methylaceto | (B.P. 74–76°/0.8 mm) | — | [81*f*] |
| Octano | 77.8–78.3 | | [32, 81*g*] |
| *p*-Methylphenylaceto | 158–159 | $H_2O$ or aq. EtOH | [81*h*] |
| *m*-Methylphenylaceto | 127–128 | $H_2O$ or aq. EtOH | [81*h*] |
| *p*-Ethylphenylaceto | 164–165 | $H_2O$ or aq. EtOH | [81*h*] |
| *p*-Bromophenylaceto | 157–158 | $H_2O$ or aq. EtOH | [81*h*] |
| *N*-Methyloctano | 15.0–17.3 | Water/ethanol 2:1 | [81*i*] |
| *p*-Methylbenzo | 142.5–143 | —[a] | [81*i*] |
| *m*-Methylbenzo | 97–98 (dec) | —[a] | [81*i*] |
| *p*-Ethylbenzo | 106.5–107 | —[a] | [81*i*] |
| *p*-Methoxybenzo | 160–160.5 | —[a] | [81*i*] |
| *m*-Methoxybenzo | 76.8–77 | —[a] | [81*i*] |
| *p*-Nitrobenzo | 178–179 (dec) | —[a] | [81*i*] |
| *m*-Nitrobenzo | 143–144 | —[a] | [81*i*] |
| *p*-Chlorobenzo | 182–183 | —[a] | [81*i*] |
| *m*-Chlorobenzo | 177–178 (dec) | —[a] | [81*i*] |

[a] Crystallized from water, methanol, ethanol, or aqueous ethanol.

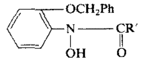
Trimethylacetohydroxamic acid was prepared from hydroxylamine and trimethylacetyl chloride in equimolar quantities [81k]. The procedure involved mixing hydroxylamine hydrochloride intimately with anhydrous potassium carbonate in ether. The mixture was placed in a large flask, then fitted with a condenser. An ether solution of the trimethylacetyl chloride was added. The water was added dropwise over a 2-hr period so that the evolution of carbon dioxide could be kept under control. Water was then cautiously run down the side of the flask. The product was taken up in ether. Ether extraction of the aqueous layer was continued until the latter no longer gave a positive ferric chloride test.

The ether extracts were dried over anhydrous magnesium sulfate, filtered, and cautiously evaporated to dryness. Yield: 70%, m.p. 154–156°C.

The ease of reacting *N*-substituted hydroxylamines with a range of acid chlorides was demonstrated by Smissman and Corbett [146]. Table VII

TABLE VII

HYDROXAMIC ACIDS FROM THE ACYLATION OF *o*-BENZYLOXYPHENYLHYDROXYLAMINE [146]



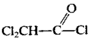
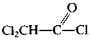
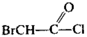
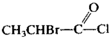
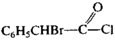
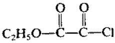
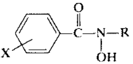
| Acylating agent | R′ | Yield, (%) | M.p.(°C) (crystallization solvent) |
|---|---|---|---|
|  $Cl_2CH{-}\overset{O}{\overset{\|}{C}}{-}Cl$ | $CHCl_2$ | 66 | 124–126 ($C_6H_6$) |
|  $Cl_2CH{-}\overset{O}{\overset{\|}{C}}{-}Cl$ | $CH_2Cl$ | 82 | 99–101 ($Et_2O$) |
|  $BrCH{-}\overset{O}{\overset{\|}{C}}{-}Cl$ | $CH_2Br$ | 87 | 96–98 ($Me_2CO—Et_2O$) |
|  $CH_3CHBr{-}\overset{O}{\overset{\|}{C}}{-}Cl$ | $CHBrCH_3$ | 79 | 125–127 ($Et_2O$) |
|  $C_6H_5CHBr{-}\overset{O}{\overset{\|}{C}}{-}Cl$ | $C_6H_5CHBr$ | 67 | 115–117 ($Me_2CO—Et_2O$) |
|  $C_2H_5O{-}\overset{O}{\overset{\|}{C}}{-}\overset{O}{\overset{\|}{C}}{-}Cl$ | $C—OC_2H_5$ | 69 | —(oil) |

TABLE VIII

*N*-SUBSTITUTED HYDROXAMIC ACIDS [81l]



| R | X | M.p., °C (crystallizing solvent) |
|---|---|---|
| i-$C_3H_7$ | H | 102–103<br>($CH_2Cl_2$-ether) |
| i-$C_3H_7$ | 2-$OCH_3$ | 131–132<br>(ethyl acetate-hexane) |
| —$CH_2$—$C_2H_5$ | 3-$OCH_3$ | 77–78<br>(ether) |
| —$CH_2$—$C_6H_5$ | 2-Br | 153<br>($CH_2Cl_2$-ether) |

gives the properties of products prepared from equimolar quantities of hydroxylamine and acid chloride in ether and in the presence of aqueous sodium bicarbonate.

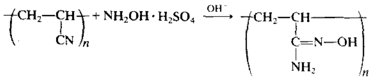
More recently, *N*-substituted hydroxylamines have been acylated with aromatic acid chlorides at 0°C in the presence of sodium bicarbonate dispersed in methylene dichloride or chloroform. The resulting products could then be *O*-acetylated and converted with Lawesson reagent to the intermediate *O*-acetylthiohydroxyamic acid and then to the corresponding thiohydroxamic acid. The preparation of the thiohydroxamic acid is said to be a one-pot preparation [81k]. Table VIII outlines the results of the hydroxamic acid preparation step.

The preparation and reaction of hydroximoyl chloride derivatives and their geometric isomerism has been studied extensively by J. E. Johnson and co-workers [81k, 81m,n,o, 143].

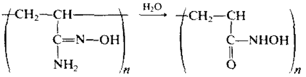
## D. Methods for Preparation of Hydroxamic Acids from Polymeric Nitriles

Fletcher and Lipowski [80, 87a] reacted polyacrylonitrile with hydroxylamines to form a polyamidoxime, which, on hydrolysis, gave a polymeric hydroxamic acid.

## *2-13. Preparation of Poly (Hydroxamic Acids)* [86, 87a]



$$\left(-CH_2-\underset{CN}{CH}-\right)_n + NH_2OH\cdot H_2SO_4 \xrightarrow{OH^-} \left(-CH_2-\underset{\underset{NH_2}{|}}{\underset{C=N-OH}{\underset{|}{CH}}}-\right)_n \qquad (31)$$



$$\left(-CH_2-\underset{\underset{NH_2}{|}}{\underset{C=N-OH}{\underset{|}{CH}}}-\right)_n \xrightarrow{H_2O} \left(-CH_2-\underset{\underset{O}{\|}}{\underset{C-NHOH}{\underset{|}{CH}}}\right)_n \qquad (32)$$

A mixture of 80 g of poly(acrylonitrile), 300 g of hydroxylamine sulfate, and 2500 ml of water, to which had been added 140 g of sodium hydroxide, is heated with stirring at 90°C for 12 hr. The mixture is cooled to room temperature, and the polymeric amidoxime is filtered off, then washed with water until the wash water is neutral.

To 20 g of the polyamidoxime is added cold 100 g of concentrated (37%) aqueous hydrochloric acid. The mixture is stirred for 5 min at 10°C and then mixed with 200 g of ice.

The gel that forms is separated, washed with deionized water and dried to a brittle poly(hydroxamic acid) containing 14.8% total nitrogen.

Vernon and Eccles first hydrolyzed crosslinked poly(acrylonitrile) with 50% sulfuric acid. The resulting polymer, after thorough washing, was treated with hydroxylamine in a sodium acetate solution and then worked up [87b,c].

## E. Alkylation of Hydroxamic Acids

The preparation of N-substituted hydroxamic acids by alkylation of appropriately substituted hydroxylamines already has been discussed. O-substituted derivatives, which are considered esters of the hydroxamic acids or hydroxamates, also may be prepared from O-alkylated hydroxylamines.

The hydroxamic acids themselves may be N-alkylated in strongly alkaline solutions, with conventional alkylating agents, such as the dialkyl sulfates or alkyl halides [87, 143]. On the other hand, $\alpha$-haloalkanoate esters in potassium hydroxide or triethylamine solutions have been used to prepare O-alkylated hydroxamic acids [87e].

## 3. MISCELLANEOUS METHODS

(1) Acylation of hydroxylamine with amides [82–85].

(2) Acylation of hydroxylamine with acylimidazoles [88].

(3) Acylation of hydroxylamine with ketenes [39, 89].

(4) Condensation of hydroxylamine with isocyanates [10, 90–95].

(5) Hydrolyses of *N*,*O*-diacylhydroxylamines to give hydroxamic acids [75].

(6) Hydrolysis of hydroximyl chlorides [96–100].

(7) The Angeli-Rimini reaction [101–103].

(8) Preparation of hydroxamic acids via reduction reactions [104–113].

(9) Preparation of hydroxamic acids by the reaction of aldehydes with arylnitroso compounds in the presence of aluminum isopropylate [104, 105].

(10) Preparation of hydroxamic acids by the oxidation of amines [20, 114].

(11) Preparation of hydroxamic acids by the oxidation of amides and lactams [115a–115d].

(12) Oxidation of aldoximes to hydroxamic acids [112, 113, 117–120].

(13) Rearrangement of nitroparaffins to alkylhydroxamic acids [121–127].

(14) The Ugi Reaction [128] (a four-component condensation).

(15) Preparation of ethyl acetohydroximate [129].

(16) Acylation of hydroxylamine with an azide [130].

(17) Nitrosation and ring expansion of 1-alkyl-3-indanones [131, 132].

(18) Cyclization of *o*-hydroxybenzohydroxamic acid [133].

(19) Reaction of nitrile oxide with diphenylketene [134].

(20) Reaction of *N*-nitrosocarbohydrazines with hydroxylamine [135].

(21) Photoreduction of nitrates in the presence of aldehydes [136].

(22) Reaction of 2,5-dimethoxy-2-($\alpha,\alpha$-dimethoxyethyl)-2,5-dihydrofuran and related compounds [137].

(23) Ring opening of *o*-nitrophenols with sulfuric acid [138].

(24) Preparation of *N*,*O*-diacylhydroxylamines from hydroxamic acids [139].

(25) Preparation of *O*-acylhydroxylamine by hydrolysis of *O*-acetylated ethyl acetohydroximate [140].

(26) Alkylation of hydroxamic acid derivatives. Treatment of potassium salts of hydroxamic acids with 1 mole of alkyl halides usually forms alkyl hydroxamates. However, in some cases small quantities of dialkylhydroxamic acid derivatives have been observed [141–142]. In some cases esters of hydroxamic esters on alkylation form N-alkylated products. However, as the chain length of the alkylating agent increases, O-alkylation also

takes place. The stereochemistry of the dialkylated products has been discussed (143).

(27) Preparation of phenyl benzohydroxamate. Unlike alkyl hydroxamates, the classical methods are unsatisfactory for the preparation of phenyl hydroxamates. A satisfactory method involves conversion of benzohydroxamic acid to the thallium(I) benzohydroxamate followed by reaction with diphenyliodonium chloride [144].

(28) Preparation of hydroxamic acids by interaction of aldehydes with sodium nitrohydroxamate [10].

(29) Preparation of dibenzoylterephthalohydroximate and *O*-alkyl hydroxamates [145].

(30) Formation of *N*-phenylhydroxamic acid by reaction of substituted nitrobenzenes with formaldehyde in aqueous acidic media [147].

(31) Acylation of hydroxylamine with carbamoyl chloride derivatives [148].

(32) Acylation of hydroxylamine with ethyl chlorocarbonate [87d].

(33) Reaction of cross-linked, chloromethylated polystyrene with diethyl malonate to form a polymeric diethyl malonate derivative used to acylate hydroxylamine to prepare a polymeric "dihydroxamic acid" [149].

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# CHAPTER 13/THIOHYDROXAMIC ACIDS

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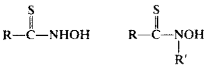
## 1. INTRODUCTION

A comprehensive review of the chemistry of thiohydroxamic acids appeared in 1971 (1).

We use the term *thiohydroxamic acid* here, as represented by structures (IA) or (IB).



$R-\overset{S}{\overset{\|}{C}}-NHOH \qquad R-\overset{S}{\overset{\|}{C}}-\underset{R'}{\underset{|}{N}}OH$

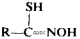
**(IA)** **(IB)**

Thiohydroxamic Acids

where R- and/or R′- may be hydrogen, alkyl groups, or aryl groups. When

R- is R″NH-, structure (IB) represents the *N*-hydroxy-*N*-alkyl (H, or aryl)-*N*′-alkyl (H, or aryl)-thioureas.

As in the case of the analogous hydroxamic acids, an equilibrium with thiohydroximic acids (structure II) has been postulated.



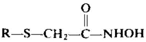
$$\mathrm{R{-}\overset{SH}{\overset{|}{C}}{=}NOH}$$

Thiohydroximic acid

(II)

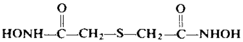
Current evidence indicates that under ordinary conditions, the hydroximic acid form does not exist at significant concentration levels. However, *S*-alkyl thiohydroximic acids are readily prepared and frequently are quite stable.

It should be pointed out that a nomenclature problem exists in connection with this class of compounds. At least one French paper uses the term "alkyl-thiohydroxamic acid" to refer to compounds of structures (III), (IV) and (V) [2a]



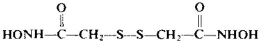
$$\mathrm{R{-}S{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}NHOH}$$

(III)



$$\mathrm{HONH{-}\overset{O}{\overset{\|}{C}}{-}CH_2{-}S{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}NHOH}$$

(IV)



$$\mathrm{HONH{-}\overset{O}{\overset{\|}{C}}{-}CH_2{-}S{-}S{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}NHOH}$$

(V)

The *Chemical Abstracts* reference to this article tacitly accepts this nomenclature. Thus an unfortunate ambiguity has developed [2b]. For our purposes in this chapter, structures (III), (IV) and (V) are simply classified as hydroxamic acids. Thiohydroxamic acids are structures represented by (IA) and (IB).

The 1987 nomenclature practice of *Chemical Abstracts* for thiohydroxamic acids is somewhat awkward for a work on functional groups. Under the present CA, system, mesitothiohydroxamic acid (see Preparation 2-5) would be indexed as "benzene, 2,4,6-trimethylcarbothioamide, -*N*-hydroxy". Acetothioydroxamic acid (see Preparation 2-1) would be indexed as "ethane, thioamide, *N*-hydroxy". In the present chapter, we retain the thiohydroxamic acid system.

The recent literature has shown the application of *N*-methylthiohydroxamic acid derivatives such as *N*-methyl-thiobutyrohydroxamic acid and higher homologous acids as photographic release agents [3].

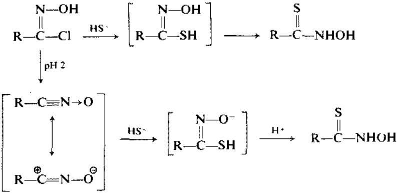
Phenylthiol phosphonates have been synthesized from *N*-alkyloxyderivatives of thiohydroxamic acids [4]. *N*-alkyl-N-α-(alkylthiophosphorothio)acyl carbamates also were synthesized using thiohydroxamic acid intermediates [5]. Both classes of compounds have been suggested as insecticides and acaricides.

Some metal chelates of thiohydroxamic acids have antibiotic properties [6, 7]. Some of these have been isolated from bacterial sources [6, 7]; other metal chelates have been synthesized [8, 9, 10].

Only a limited number of procedures seem to be available for the preparation of this class of compounds. Many of the procedures suffer from poor yields and the formation of complex by products.

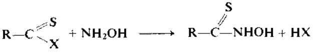
Because all the methods of synthesis mentioned in this chapter are condensation reactions, we have subdivided the syntheses into (A) preparations in which the carbon-sulfur double bond is established; (B) reactions in which the carbon-nitrogen bond of a thiohydroxamic acid is established.

Among the methods for the formation of the carbon-sulfur double bond are the reaction of hydroximyl chloride with hydrogen sulfide ions and of nitrile oxides with hydrogen sulfide ions (Eq. 1). The source of hydrogen sulfide ions may be solutions of sodium sulfide formed directly from the salts, or generated by adding hydrogen sulfide to caustic solutions or by the use of thiourea.



(1)

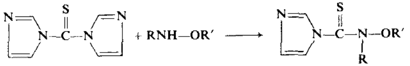
The methods involving the formation of carbon-nitrogen bonds include the thioacylation of hydroxylamine with salts of dithiocarboxylic acids, esters of dithiocarboxylic esters (particularly carboxymethyl dithiocarboxylates), esters of thiocarboxylic acids, and thiocarboxylic chlorides (Eq. 2).



$$\mathrm{R{-}C}\overset{\displaystyle\nearrow S}{\underset{\displaystyle\searrow X}{}} + \mathrm{NH_2OH} \longrightarrow \mathrm{R{-}}\overset{S}{\overset{\|}{\mathrm{C}}}\mathrm{{-}NHOH + HX} \qquad (2)$$

$X = {-S^-},\ {-S{-}R'},\ {-O{-}R'},$ or Cl

A related thioacylation makes use of *N,N'*-thiocarbonyldiimidazole (Eq. 3).


(3)

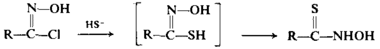
A method that is of considerable importance is the addition of hydroxylamine and substituted hydroxylamines to isothiocyanates [11–15]. This approach leads to substituted *N*-hydroxythioureas.

## 2. CONDENSATION REACTIONS

### A. Preparation of Thiohydroxamic Acids by Establishment of the Carbon–Sulfur Double Bond

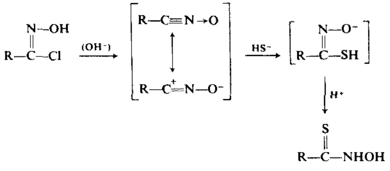
Those methods of preparation of thiohydroxamic acids in which the carbon-sulfur double bond is established obviously have the advantage of requiring organic starting materials which are somewhat more accessible than the carbon-sulfur compounds required for the alternative syntheses in which the carbon-nitrogen bond has to be prepared. Furthermore, relatively simple inorganic sulfur compounds are the usual coreactants.

One of the methods of preparation is the reaction of hydroximyl chlorides with sodium hydrogen sulfide. While this reaction appears to be quite straight-forward (Eq. 4), that is, a nucleophilic attack by a hydrosulfide


(4)

$$\mathrm{R{-}\overset{\overset{N{-}OH}{\|}}{C}{-}Cl} \xrightarrow{HS^-} \left[\mathrm{R{-}\overset{\overset{N{-}OH}{\|}}{C}{-}SH}\right] \longrightarrow \mathrm{R{-}\overset{\overset{S}{\|}}{C}{-}NHOH} \tag{4}$$

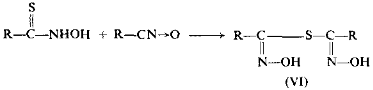
ion, hydroximyl chlorides are dehydrohalogenated at pH 2 to form nitrile oxides [1]. Since nitrile oxides also react with hydrosulfide ions to produce thiohydroxamic acids (Eq. 5), it may be difficult to determine the exact


(5)

$$\mathrm{R{-}\overset{\overset{N{-}OH}{\|}}{C}{-}Cl} \xrightarrow{(OH^-)} \left[\begin{array}{c}\mathrm{R{-}C{\equiv}N{\rightarrow}O}\\ \updownarrow \\ \mathrm{R{-}\overset{+}{C}{=}N{-}O^-}\end{array}\right] \xrightarrow{HS^-} \left[\mathrm{R{-}\overset{\overset{N{-}O^-}{\|}}{C}{-}SH}\right] \xrightarrow{H^+} \mathrm{R{-}\overset{\overset{S}{\|}}{C}{-}NHOH} \tag{5}$$

course of the reaction. For our purposes, we merely assume that these considerations allow us to use two different starting materials for these preparations (Eqs. 4, 5).

At pH 8, a second mole of nitrile oxide may add to thiohydroxamic acids to form thiohydroximic acid anhydrides (structure VI, Eq. 6).



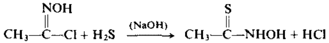
$$R-\overset{\overset{S}{\|}}{C}-NHOH + R-CN\rightarrow O \longrightarrow \underset{\underset{N-OH}{\|}}{R-C}-S-\underset{\underset{N-OH}{\|}}{C}-R \qquad (6)$$

(VI)

When mercaptans are substituted for hydrogen sulfide in the aforementioned reactions, *S*-alkyl thiohydroximic acids are formed.

The reaction of hydroximyl chlorides with hydrosulfide ions should be carried out in an excess of sodium hydrogen sulfide to prevent desulfurization side reactions [1]. The use of alcoholic hydroximyl chloride in the example seems to be quite a common matter. We would suggest exploration of the use of an inert solvent in this reaction.

## *2-1. Preparation of Acetothiohydroxamic Acid* [1, 17]



$$CH_3-\overset{\overset{NOH}{\|}}{C}-Cl + H_2S \xrightarrow{(NaOH)} CH_3-\overset{\overset{S}{\|}}{C}-NHOH + HCl \qquad (7)$$

**CAUTION:** Hydrogen sulfide is considered a highly toxic gas. All due precautions must be taken in handling this gas and its solutions. The disposition of excess hydrogen sulfide and of its solutions must also follow all appropriate safety measures.

In a well-ventilated hood, 375 ml of 1 *N* aqueous sodium hydroxide cooled to 0°C is saturated with hydrogen sulfide.

While this solution is cooled with running water, with vigorous stirring, 140 ml of an approximately 5% solution of acetohydroxamyl chloride (7 gm, 0.0075 mole) in ethanol is added over a 45 min period. After standing at room temperature for 15 min, the clear solution is extracted five times with 100-ml portions of ether to remove the ethanol.

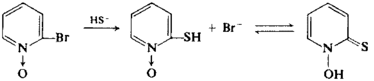
While cooling the material in an ice-salt bath, with vigorous stirring, the aqueous layer is cautiously acidified with conc. hydrochloric acid. The product is extracted with five 80 ml portions of ether. The ether extracts are combined and dried over calcium chloride in the dark and, after filtration, evaporated to near dryness in a rotary evaporator. The residue is extracted with 10 ml of ether. The extract is evaporated at 0.2 mm Hg at 20°C. After approximately 30 min, the product crystallizes to afford 2 gm (29%), m.p. 30°C. This product is not very stable. It decomposes even at −20°C.

Freshly prepared, the product exhibits a single spot on thin-layer chromatography on silicagel (Kieselgel GF 254; chloroform: methanol, 70/30 v/v). The spot is made visible with ferric chloride solution (blue color).

It will be recalled from Chapter 12, Hydroxamic Acids, that 2-hydroxypyridine *N*-oxides are considered tautomers of cyclic hydroxamic acids. Therefore, 2-halopyridine *N*-oxides are closely related to cyclic hydroximyl halides. Indeed, with such reagents, cyclic thiohydroxamic acids have been prepared. In this case, the carbon-sulfur double bond has been formed using sodium hydrogen sulfide, sodium sulfide, or thiourea [18]. The use of thiourea instead of hydrogen sulfide has much to recommend it in terms of convenience. However, thiourea is a "cancer suspect agent" and must be handled with due care.

When thiourea is used, the first isolated product from this reaction is an isothiourea complex. Care must be taken to convert this intermediate to the free product.

### *2-2. Preparation of* N*-Hydroxy-2-pyridinethione* [18]

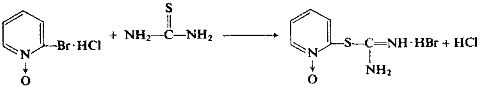


(8)

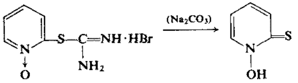
A solution of 60 gm (0.284) of 2-bromopyridine *N*-oxide hydrochloride is neutralized with 25% aqueous sodium hydroxide. In a well-ventilated hood, to this solution, heated with stirring on a steam bath, is added dropwise over a 1-hr period a solution of 32 gm (0.57 mole) of sodium hydrogen sulfide in 150 ml of water. After the addition has been completed, heating is continued for 0.5 hr. The reaction mixture is cooled, filtered, and acidified with 6 *N* hydrochloric acid to afford 24 gm (67%), m.p. 65–68°C. Upon recrystallization from aqueous ethanol, the melting point is raised to 68–70°C.

Similar results were obtained when an equivalent quantity of sodium sulfide was substituted for sodium hydrogen sulfide.

### *2-3. Preparation of N-Hydroxy-2-pyridinethione (Using Thiourea)* [18]



(9)



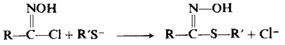
(10)

**CAUTION:** Thiourea is a cancer suspect agent.

A solution of 19.4 gm (0.09 mole) of 2-bromopyridine *N*-oxide hydrochloride and 9.7 gm (0.128 mole) of thiourea in 300 ml of absolute ethanol is refluxed for 1 hr. The precipitated 2-pyridyl *N*-oxide isothiourea hydrobromide is filtered off to afford *18* gm *(80%)*, m.p. *160–160.5°C* (dec.). Upon recrystallization from absolute ethanol, the melting point remains unchanged.

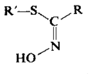
A solution of 12.5 gm (0.05 mole) of the above thiourea addition compound and 10 gm of sodium carbonate in 125 ml of water is allowed to stand at room temperature for 4 hr. Upon careful acidification with 20% aqueous hydrochloric acid, 5 gm (79%) of *N*-hydroxy-3-pyridinethione is isolated, m.p. 65–67°C (overall yield, 63%).

When hydroximyl chlorides are reacted with mercaptans in caustic solution (e.g., sodium methylate in methanol) [19] or in the presence of triethylamine [20] *S*-alkyl thiohydroximates form (Eq. 11). The stereoisomerism of these compounds has been examined. Usually, the synthesis



$$\mathrm{R{-}\overset{\overset{\displaystyle NOH}{\|}}{C}{-}Cl + R'S^- \longrightarrow R{-}\overset{\overset{\displaystyle N{-}OH}{\|}}{C}{-}S{-}R' + Cl^-} \qquad (11)$$

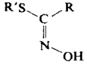
results in the formation of a single isomer, the thermodynamically more stable Z-isomer (VII). The E-isomer (VIII) may be produced by irradiation of the Z-isomer with ultraviolet light [19]. Because these compounds



Z-*S*-Alkyl hydroxymate

("α" or "*syn*" isomer)

(VII)



E-*S*-Alkyl hydroximate

("β" or "*anti*" isomer)

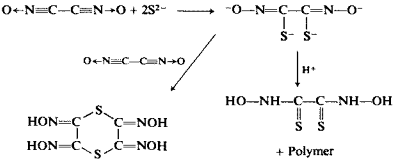
(VIII)

are, strictly speaking, not thiohydroxamic acids, no representative preparation is given here. Davis et al. [19] and Exner et al. [20] give experimental details for the synthesis of these derivatives.

As stated previously, hydroximyl chlorides, at $pH > 2$ are dehydrohalogenated to form nitrile oxides. Evidently, aliphatic hydroximyl chlorides may eliminate the elements of hydrogen chloride at −15°C in an inert solvent [21]. Many aliphatic nitrile oxides are said to be unstable; hence, only in isolated cases have these been used as starting materials for the synthesis of thiohydroxamic acids [22]. Aromatic nitrile oxides, particularly 2, 6-disubstituted aromatic nitrile oxides, react with mercaptans and with sulfide ions [23, 24]. With mercaptans, *S*-alkyl thiohydroximic acids form; with sodium sulfide, the sodium salts of thiohydroxamic acids are isolated. If the pH of the reaction is kept below 8, a mixture of products is formed consisting of the sodium salt of the thiohydroxamic acid and a thiohydroximic acid anhydride. The latter product also forms if sodium hydrogen sulfide is used instead of sodium sulfide [23].

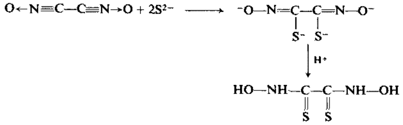
In the preparation of oxalobis(thiohydroxamic) acid, the yield is quite low. In part, this may be a general characteristic in the preparation of aliphatic thiohydroxamic acids. It may also be due to the choice of solvents. The product formation is accompanied by the reaction of the product with an excess of starting material, to form a cyclic anhydride, tetroximino-1,4-dithane (Eq. 12). The bulk of the starting material seems to be converted to a high molecular weight polymer. We suggest that the following modifications be considered for this preparation in an effort to improve yields.

1. The carbon tetrachloride solution of the organic reagent be added slowly to the sodium sulfide solution with vigorous stirring. (**CAUTION:** Carbon tetrachloride is a suspected carcinogenic agent, and all due precautions must be taken in handling and disposing of this compound.)
2. The effect of reaction temperature be explored.
3. The use of a cationic surfactant or of a phase transfer agent be considered.



(12)

### *2-4. Preparation of Oxalobis(thiohydroxamic) Acid* [22]



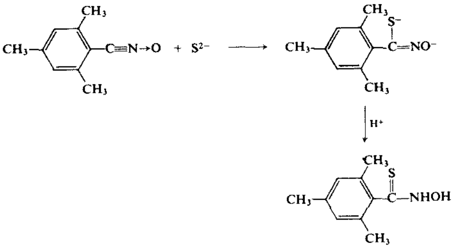
(13)

In a well-ventilated hood at 0°C, a solution of 0.45 gm (0.00545 mole) of dicyano di-*N*-oxide in 50 ml of carbon tetrachloride (**CAUTION:** Cancer suspect agent) is vigorously stirred with an aqueous solution containing 2.4 gm (0.025 mole) of sodium sulfide monohydrate for 1 hr. The organic phase is discarded. The aqueous solution is acidified with 2 *N* sulfuric acid and extracted three times with 50-ml portions of ether. The ether extracts are combined and evaporated to a volume of 30 ml.

To this solution is added 15 ml of ligroin. A precipitate of 170 ml of tetra-oximino-1,4-dithiane precipitates. After filtration, the filtrate is stored for 4 days. During this time oxalodithiohydroxamic acid separates as large yellow crystals and is filtered to afford 210 mg (12%), m.p. 123–125°C.

In the aromatic series, some nitrile oxides dimerize to furoxans; however, nitrile oxides which are sterically hindered in the two ortho positions, will react with mercaptans and sulfides under appropriate conditions [23].

### *2.5. Preparation of Mesitothiohydroxamic Acid* [23, 24]



(14)

In a well-ventilated hood, a solution of 0.6 gm (0.00372 mole) of mesitonitrile *N*-oxide in 50 ml of ether is vigorously stirred at 25°C for 5 hr with a solution of 5.6 gm (0.0217 mole) of sodium sulfide decahydrate. The mixture is acidified with diluted sulfuric acid, the ether layer is separated and combined with ether extracts of the aqueous phase (using two 50-ml portions of ether). Upon evaporation of the solvent, the residue is a mixture of sulfur and crude mesitothiohydroxamic acid. The latter is extracted with petroleum ether. The residue from the evaporation of the petroleum ether extracts is filtered to afford 0.67 gm (92%), m.p. 91–92°C.

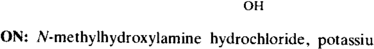
## B. Notes on the Preparation of Thiohydroxamic Acids by Establishment of the Carbon–Nitrogen Bond

The reaction for the synthesis of thiohydroxamic acids in which the carbon-nitrogen bond has to be formed are primarily thioacylations of hydroxylamine or substituted hydroxylamines. At least formally these reactions frequently resemble the analogous acylation reactions used for the preparation of hydroxamic acids. The availability of thioacylating agents is more limited of course. On the other hand, a few thioacylating agents exist which have no counterpart among the acylating agents.

While dithiocarboxylic acids (dithioic acids) are sensitive to oxidation, their salts have been used to prepare thiohydroxamic acids. The use of potassium dithioformate, the first member of this series of salts, is illustrated in Preparation 2-6.

The compound *N*-methyl-*N*-thioformyl hydroxylamine, *N*-methylformothiohydroxamic acid, sometimes called "thioformin" [6] or "fluopsin" [9], has been isolated from bacteria such as *Pseudomonas fluorescens* [6]. The compound readily forms chelates with iron (III) or copper (II). The ability of these compounds to form metal chelates is of interest because of their involvement in bacterial iron-transport systems [8, 9]. The complexes have also been used to isolate and purify crude *N*-alkylthiohydroxamic acids [7].

### *2-6. Preparation of N-Methyl-N-thioformylhydroxylamine (N-Methylformothiohydroxamine Acid)* [6]



$$CH_3NHOH\ .HCl + K\,(HCS_2) \longrightarrow CH_3-\underset{\underset{OH}{|}}{N}-\overset{\overset{S}{\|}}{C}-H + KCl + H_2S \qquad (15)$$

**CAUTION:** *N*-methylhydroxylamine hydrochloride, potassium dithioformate, and hydrogen sulfide are hazardous materials and must be handled with proper precautions.

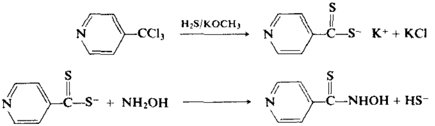
In a well-ventilated hood, with appropriate safety precautions, a well-stirred solution of 1.16 g (1.4 millimoles) of *N*-methylhydroxylamine hydrochloride in 10 ml of deionized water is reacted with 5 ml of a red solution of 1.91 g (16.5 millimoles) of potassium dithioformate at room temperature for approximately 1 hr. During this time, the reaction mixture foams ($H_2S$ being evolved) and gradually becomes colorless.

The reaction mixture is extracted four times with 20-ml portions of ethyl acetate. The ethyl acetate extract is concentrated under reduced pressure. The syrupy residue is distilled under reduced pressure to afford 380 mg of thioformin, b.p. 52°C/3 mm. Yield: 30%.

In the preparation of the homolog, *N*-ethyl-*N*-thioformylhydroxylamine, the reaction mixture is first adjusted to pH 1 with concentrated hydrochloric acid. The product is extracted with chloroform instead of ethyl acetate. After evaporation of the chloroform extract to dryness, the crude product is redissolved in fresh chloroform and shaken with an aqueous solution of cupric sulfate to form the copper complex of the product. The complex, being soluble in the organic layer, is extracted into the chloroform layer. The chloroform layer is separated. The free thiohydroxamic acid is obtained by treating the chloroform solution with hydrogen sulfide to precipitate cupric sulfide. The product is removed from the chloroform solution by evaporation of the solvent, followed by distillation under reduced pressure. The boiling point of *N*-ethyl-*N*-thioformylhydroxylamine is 68–69°/5 mm [7].

Table I (based on [6] and [7]) gives some physical properties of *N*-substituted formothiohydroxamic acids. Two examples for forming the carbon-nitrogen bond are given here, one using a potassium dithiocarboxylate, the other using a Grignard reaction.

### 2-7. *Preparation of γ-Pyridylthiohydroxamic Acid* [25]



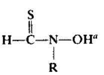
(16)

(17)

(*a*) *Preparation of potassium dithioisonicotinate.* A solution of 80 gm (2.05 gm-atoms) of potassium in 1.5 liters of methanol is prepared. One-half of this solution is saturated with hydrogen sulfide and then combined with the other half of the solution. To this, under a nitrogen atmosphere, is added slowly, at such a rate that the reaction temperature never exceeds

TABLE I

PROPERTIES OF *N*-SUBSTITUTED FORMOTHIOHYDROXAMIC ACIDS



$$H{-}\overset{\overset{\displaystyle S}{\|}}{C}{-}\underset{\underset{\displaystyle R}{|}}{N}{-}OH^{a}$$

| R | B.p.,°C/mm | M.p.,°C |
|---|---|---|
| $CH_3$– | 52/3 | — |
| $C_2H_5$– | 68–69/5 | — |
| $CH_3$<br>CH—<br>$CH_5$ | 66–67/5 | — |
| Cyclohexyl | — | 92–94 |
| Phenyl | — | 70–71 |
| Benzyl | | 49–50 |
| *p*-Chlorobenzyl | | 99–100 |

[a] Based on [6] and [7].

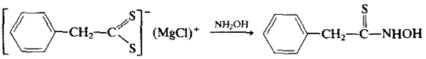
60°C, solution of 100 gm (0.51 mole) of γ-trichloromethylpyridine in methanol. The mixture is maintained at room temperature for 24 hr under nitrogen. Then the precipitated potassium chloride is filtered off. The filtrate is evaporated under reduced pressure to a small volume. If necessary, potassium chloride may again have to be filtered off. The product is precipitated from the filtrate by adding the methanolic filtrate to a large volume of ether. Yield of crude intermediate 74 gm. To purify this product, it is taken up in approximately 250 ml of cold methanol, freed of potassium chloride, reprecipitated with 1.5 liters of ether and filtered to afford 52 gm (53%), m.p. 270°C (dec.) (dark red-brown needles).

(*b*) *Preparation of γ-pyridylthiohydroxamic acid.* A well-stirred mixture of 39 gm (0.202 mole) of potassium dithioisonicotinate 21 gm (0.303 mole) of hydroxylamine hydrochloride, and 62 gm of anhydrous potassium carbonate in 250 ml of water is heated at reflux for 6 hr. After cooling, the pH of the mixture is adjusted with 10% aqueous hydrochloric acid to 8.0, the precipitated sulfur is filtered off, and the filtrate is further acidified to the range of 4.0–5.5. The yellow-brown precipitate is filtered off to afford 22.5 gm (72%). The product may be purified by dissolving it in a minimum quantity of cold 1 *N* aqueous sodium hydroxide, treating with charcoal, filtering, and acidifying the filtrate to pH 4–5.5 with 10%

aqueous hydrochloric acid. If necessary this step may be repeated. The melting point of the product is approximately 180°C (dec.).

The preparation of phenylacetothiohydroxamic acid from magnesium dithiophenylacetate chloride was generally described in Ettlinger and Lundeen [26] and in greater detail in Walter and Schaumann [1] and Walter and Heider [17].

### 2-8. *Preparation of Phenylacetothiohydroxamic Acid* [1, 17]



(18)

In a hood, to a suspension in ether of 0.33 mole of magnesium dithiophenylacetate chloride (prepared by treating benzylmagnesium chloride with carbon disulfide in ether) is added dropwise and with stirring at ice temperature a solution of 22 gm (0.32 mole) of hydroxylamine hydrochloride and 17 gm (0.16 mole) of sodium carbonate in 250 ml of water. During this addition, the magnesium salt goes into solution, hydrogen sulfide evolves, and the ether layer becomes red-brown.

After the addition has beeen completed, the aqueous layer is separated and preserved. The other layer is discarded.

The aqueous solution is freed from sulfur by filtration and acidified with ice-cold 2 *N* sulfuric acid until distinctly acidic. During this stage the crude product separates partially as an oil. The product is separated from the aqueous phase by extraction with five 70 ml portions of ether. The combined extracts are dried with calcium chloride and concentrated at 25°C. The residual oil gradually crystallizes, and after recrystallization from benzene-petroleum ether affords 16.6 gm (33%), m.p. 73–74.2°C.

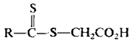
Murray and co-workers [8], using a similar procedure, gave the melting point of phenylacetothiohydroxamic acid as 73–74°C. They also report NMR 7.8, br, NHOH; 7.3 s, $C_6H_5$; 3.9, s, $CH_2$. Mass spectrum (m/e) 167 (parent on $C_8H_9NOS^+$), 150 ($C_8H_7NS^+$), 134 ($C_8H_8NO^+$), 117 ($C_7H_7CN^+$), 91 ($C_6H_7^+$), 77 ($C_6H_5^+$).

By the same technique, benzothiohydroxamic acid was prepared in a 26% yield as a yellow-green oil. Using the technique of Jensen and coworkers (27), (Preparation 2-9), Murray and co-workers obtained benzothiohydroxamic acid in a 76% yield.

The preparation of acetothiohydroxamic acid, by use of a Grignard reagent, even when operating at ice temperatures as rapidly as possible led to an unstable oil (see also Preparation 2-1). An attempt to prepare 1-naphthothiohydroxamic acid from 1-naphthylmagnesium bromide and carbon disulfide led to a dithio-1-naphthoic acid (identified by spectrum), which rapidly decomposed to form a crystalline disulfide, m.p. 165°C. Attempts to convert the dithio acid to the thiohydroxamic acid resulted in the formation of a brown oil that decomposed rapidly at room temperature. The oily acid did, however, show the characteristic bands of thiohydroxamic acids.

Whereas the acylation of hydroxylamine with esters of carboxylic acids is among the oldest and the most widely used method for the preparation of hydroxamic acids, the use of esters of thiocarboxylic and dithiocarboxylic acids seems to be a relatively recent development.

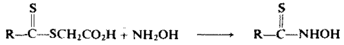
The carboxymethyl dithiocarboxylates (also named "carboxymethyl dithioates" or "thioacylglycolic acid esters") are readily prepared and



$$R-\overset{\overset{S}{\|}}{C}-S-CH_2CO_2H$$

stable. This class of compounds may be considered to be activated esters. Compounds in which the R group is aliphatic or heterocyclic are said to react rapidly with hydroxylamines and substituted hydroxylamines, whereas aromatic dithioate esters react sluggishly [27]. While the method is said to be of wide applicability for the preparation of thiohydroxamic acids, in a few cases, the isolated products were nitriles [27].

### *2-9. Generalized Preparation of Thiohydroxamic Acids from Carboxymethyl Dithioates* [27]



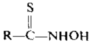
$$R-\overset{\overset{S}{\|}}{C}-SCH_2CO_2H + NH_2OH \longrightarrow R-\overset{\overset{S}{\|}}{C}-NHOH \qquad (19)$$

To a solution of 10 mmole of a carboxymethyl dithioate in 10 ml of 1 $N$ sodium hydroxide is added a solution of 11 mmoles of hydroxylamine hydrochloride in 11 ml of 1 $N$ sodium hydroxide with cooling and in such a manner that the pH finally remains at pH 7 (if necessary aqueous sodium hydroxide or acetic acid is added). The reddish color of the reaction mixture disappears more or less rapidly. To complete the reaction, the mixture is stirred at room temperature for 2 to 24 hr. Then the reaction mixture is acidified with acetic acid and the crude product is extracted with ether.

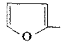
The combined ether extracts are washed with water, dried with magnesium sulfate, filtered, and evaporated under reduced pressure. The crude residue, which contains unreacted starting materials, is recrystallized from benzene-petroleum ether (2:3) or ether-petroleum ether (1:1) until the

TABLE II

PROPERTIES OF THIOHYDROXAMIC ACIDS[a]



$$R-\overset{\overset{\displaystyle S}{\|}}{C}-NHOH$$

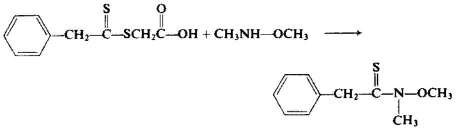
| R = | M.p. (°C) | R = | M.p. (°C) |
|---|---|---|---|
| $C_6H_5$ | 121–122 | *p*-*i*-$C_3H_7OC_6H_4$ | 80–81 |
| *p*-$ClC_6H_4$ | 91–92 | *o*-*n*-$C_4H_9OC_6H_4$ | 91–92 |
| *o*-$CH_3OC_6H_4$ | 76.5–77 | | |
| *p*-$CH_3OC_6H_4$ | 117–118 |  | 92–93 |
| *o*-*m*-$C_3H_7OC_6H_4$ | 59–60 | $C_6H_5-CH_2$ | 72–73 |

[a] From Jensen *et al.* [27].

infrared spectra shows no absorption at 1700 cm$^{-1}$. The products are colorless or light yellow. Table II [27] lists a number of thiohydroxamic acids prepared by this technique.

By using this technique, Murray and co-workers [8] prepared benzothiohydroxamic acid in a 76% yield, but only as a yellow oil. (Jensen and co-workers [27] give a m.p. of 72–73°C; Table II.) Their *p*-tolylthiohydroxamic acid was reported to have a m.p. of 47–49°C. Their *p*-methoxyphenylthiohydroxamic acid was m.p. 117–118°C, *p*-chlorophenylthiohydroxamic acid was m.p. 91–92°C, and 2-furanthiohydroxamic acid was m.p. 92–93°C, which agree with the properties given in Table II. The preparation of *N*-methylbenzothiohydroxamic acid by the procedure of Jensen and co-workers led to a yellow oil, NMR ($CDCl_3$) 10.4, br, NHOH; 7.4, s, $C_6H_5$; 3.5 s, $CH_3$. Mass spectrum m/c 167 (parent $C_8H_9NSO^+$), 166 ($C_8H_8NSO^+$), 150 ($C_8H_8NS^+$). 121 ($C_6H_5CS^+$) [9].

Using carboxymethyl dithioates with *N,O*-dialkylhydroxylamines, the analogous reaction produces O-alkyl esters of *N*-alkyl thiohydroxamic acids [1, 28] (Eq. 20). The (alkoxythiocarbonyl)thioacetic acids (also called "*O*-alkyl *S*-carboxymethyl dithiocarbonates") behave in an analogous manner to form *O*-alkyl *N*-hydroxythiocarbamates [29]. It is interesting to note that in this reaction a competitive system is at hand, i.e., the possibility of substitution of either an R—O or an HOOC—$CH_2$—S—bond exists. Judging from the high yields reported (87–98%), the carbon-sulfur bond reacts preferentially (Eq. 21).



(20)

Methyl *N*-methylphenylacetothiohydroximate,
b.p. 107°–109°C/0.05 mm Hg

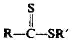
### *2-10. Generalized Preparation of* O*-Alkyl* N*-Hydroxythiocarbamates* [29]

$$RO-\overset{\overset{S}{\|}}{C}-S-CH_2CO_2H + NH_2OH \longrightarrow RO-\overset{\overset{S}{\|}}{C}-NHOH + HSCH_2CO_2H \qquad (21)$$

To a solution cooled to 0°C of 0.02 mole of an [(alkoxythiocarbonyl)-thio]-acetic acid in 20 ml of 1 *N* sodium hydroxide is added a solution of 0.02 mole of hydroxylamine hydrochloride dissolved in 19 ml of 1 *N* sodium hydroxide. Then 50 ml of ether is added (for higher homologs a larger quantity of ether is used). The combined mixture is placed in a separatory funnel and 20 ml of 1 *N* sodium hydroxide is added. The ether layer is immediately separated from the aqueous phase and preserved. The aqueous phase is extracted two times with 25 ml portions of ether.

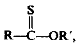
The ether extracts are combined, washed two times with 3-ml portions of water, dried with magnesium sulfate for 1 hr, and filtered. Upon evaporation under reduced pressure, the residue is considered the product. Where R = butyl, isobutyl, or hexyl, the products are oils. Where R = nonyl or undecyl, the products are low-melting solids after recrystallization from hexane (R = nonyl, m.p. 42–43.5°C; R = undecyl, m.p. 51.5–52°C).

A recent patent mentions the formation of thiohydroxamic acids not only by the reaction of hydroxylamine with ordinary esters of dithiocarboxylic acids (IX) ("dithioic acids"), but also of thiocarboxylic acids (X) ("thioic acids") where R′ may be $C_2H_5$. The reactions are carried out in the presence of alcoholates [30].



$$R-\overset{\overset{S}{\|}}{C}-SR'$$

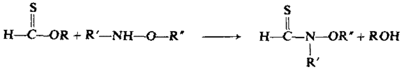
(IX)



$$R-\overset{\overset{S}{\|}}{C}-OR',$$

(X)

*O*-Ethyl thioformate reacts with *N*,*O*-disubstituted hydroxylamines in the expected manner [1, 28] (Eq. 22).



$$H-\overset{\overset{\displaystyle S}{\|}}{C}-OR + R'-NH-O-R'' \longrightarrow H-\overset{\overset{\displaystyle S}{\|}}{C}-\underset{\underset{\displaystyle R'}{|}}{N}-OR'' + ROH \qquad (22)$$

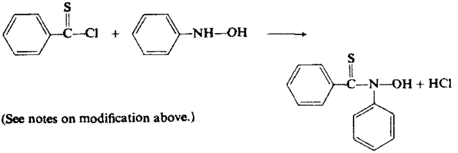
At one time, it was thought that this reaction was limited to one involving *O*-substituted hydroxylamines. Products derived from *N*-substituted hyroxylamines were thought to be unstable [1]. However, as shown in Table I, for example, *N*-substituted formothiohydroxaminic acids are known and stable; therefore reaction of *O*-ethylthioformate with all substituted hydroxylamines ought to be reevaluated.

Because the acid chlorides of thiocarboxylic acids are either unstable or inaccessible, their utilization in the preparation of thiohydroxamic acids is limited. An example of this method, using thiobenzoyl chloride, is given in Preparation 2-10. This method [31] has been modified subsequently to give an improved yield [32]. Unfortunately, the details of the modifications are not quite specific enough to include in the description of the method. Therefore, we give the modifications ahead of the description, to alert the reader to them.

*Modifications suggested for Preparation 2-11* [32]. 1. After the slow addition of the Grignard reagent to carbon disulfide, the reaction is stirred for 3–5 hr prior to the work-up. This is said to increase the yield of dithiobenzoic acid.

2. After completion of the reaction of thiobenzoyl chloride and phenylhydroxylamine, the product is extracted from the ether layer with concentrated aqueous ammonia. The free thiohydroxamic acid is precipitated from its ammonium salt solution by neutralizing the solution slowly, at the temperature of an ice-salt bath, with cold 3 *N* hydrochloric acid. The precipitated product is recrystallized from ethanol to afford 24 gm, m.p. 101–102°C.

### *2-11. Preparation of* N*-Phenylbenzothiohydroxamic Acid* [17]



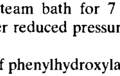
(23)

(See notes on modification above.)

To a solution of 154 gm of carbon disulfide in 30 ml of anhydrous ether is added, under nitrogen, a solution of phenylmagnesium bromide (prepared from 240 gm of phenyl bromide in 600 ml of anhydrous ether and 33 gm of magnesium). After standing overnight, the reaction mixture is cautiously acidified with 25% aqueous hydrochloric acid. The dithiobenzoic acid is extracted from the reaction mixture with ether. To the ether extract containing dithiobenzoic acid is added 83 gm of thionyl chloride. The mixture is warmed on a steam bath for 7 hr. The purple thiobenzoyl chloride is distilled off under reduced pressure between 150 and 220°C to afford 19.2 gm.

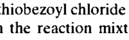
To 19.6 gm (0.18 mole) of phenylhydroxylamine in a minimum quantity of ether is added the crude thiobezoyl chloride as quickly as its characteristic color is discharged from the reaction mixture. The yellow solution is then evaporated under reduced pressure until crystallization starts. The mixture is stored in a refrigerator to permit completion of the crystallization process. The crude product is recrystallized from ethanol-water to afford 3–4 gm, m.p. 102–103°C.

By use of *O*-ethyl thiochlorocarbonate,

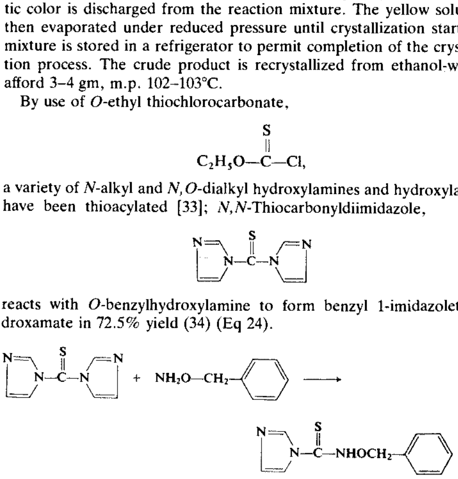


$$C_2H_5O{-}\overset{\overset{\displaystyle S}{\|}}{C}{-}Cl,$$

a variety of *N*-alkyl and *N,O*-dialkyl hydroxylamines and hydroxylaminals have been thioacylated [33]; *N,N*-Thiocarbonyldiimidazole,



reacts with *O*-benzylhydroxylamine to form benzyl 1-imidazolethiohydroxamate in 72.5% yield (34) (Eq 24).



(24)

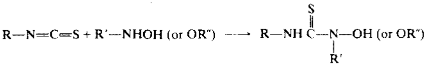
It is interesting to speculate whether the thioacylimidazole may be useful as a thioacylating agent for hydroxylamines, much as the acylimidazoles have been used to prepare hydroxamic acids (see Chapter 12, Hydroxamic Acids).

## *2-12. Preparation of Hydroxythiourea Derivatives*

By reaction of isothiocyanates with appropriately substituted hydroxylamine derivatives, a variety of *N*-hydroxy (or *N*-alkoxy) thioureas have been prepared [11, 12, 13, 14, 16]. Two general methods of synthesis have been described [16]. In Method A, to a solution of the hydroxylamine in dry ether or a mixture of benzene and petroleum ether at −15°C the isothiocyanate is added dropwise, with stirring. The reaction mixture is then briefly warmed to room temperature and then again cooled to crystallize the product out. In some case, the product had to be distilled cautiously, using a short-vapor-path still.

When the product was difficult to produce in crystalline form, Method B may be used. This consisted of adding a benzene solution of the hydroxylamine to a solution of the isothiocyanate dissolved in petroleum ether at −15°C. The resulting precipitate is then promptly recrystallized from ethyl acetate.

Equation 25 outlines the general reaction sequence.

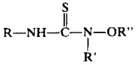


$$R{-}N{=}C{=}S + R'{-}NHOH\ (\text{or } OR'') \longrightarrow R{-}NH\overset{\overset{S}{\|}}{C}{-}\underset{\underset{R'}{|}}{N}{-}OH\ (\text{or } OR'') \qquad (25)$$

Table III outlines the properties of some of the thiourea derivatives prepared by these two procedures.

TABLE III

Preparations and Properties of Substituted Hydroxythiourea [16]



$$R{-}NH{-}\overset{\overset{S}{\|}}{C}{-}\underset{\underset{R'}{|}}{N}{-}OR''$$

| R | R′ | R″ | Method of Preparation | Yield (%) | M.p.,°C. |
|---|---|---|---|---|---|
| $C_6H_5$ | 2,4,6-$(CH_3)_3C_6H_2$ | H | B | 42 | 137 |
| 2,6-$(CH_3)_2C_6H_3$ | 2,4,6-$(CH_3)_3C_6H_2$ | H | A | 28 | 258 |
| 2,6-$(CH_3)_2C_6H_3$ | $C_6H_5$ | H | A | 42 | 131 |
| $CH_3$ | 2,4,6-$CH_3)_3C_6H_2$ | H | A | 64 | 135 |
| 2,6-$(CH_3)_2C_6H_3$ | $CH_3$ | H | A | 46 | 117.5 |
| $C_6H_5$ | $CH_3$ | H | B | 67 | 123 |
| $(CH_3)_3C$ | $CH_3$ | H | B | 69 | (oil) |
| $C_6H_5$ | $CH_3$ | $CH_3$ | A | 82 | (oil) |
| 2,6-$(CH_3)_2C_6H_4$ | $CH_3$ | $CH_3$ | A | 63 | 101 |

## 3. MISCELLANEOUS METHODS

(1) Reaction of hydroximyl chlorides with thionate salts [15].

(2) Reaction of primary aliphatic nitro compounds with aliphatic or aromatic mercaptans, under pressure, in the presence of base [1].

(3) O-acylthiohydroxamic acids—a review of structure and radical chain reactions [35].

(4) Use of Lawesson's reagent to convert O-acetylated hydroxamic acids to thiohydroxamic acids [36].

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